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VOLUME XV SEPTEMBER 1958 NUMBER 5

JOURNAL OF NEUROSURGERY

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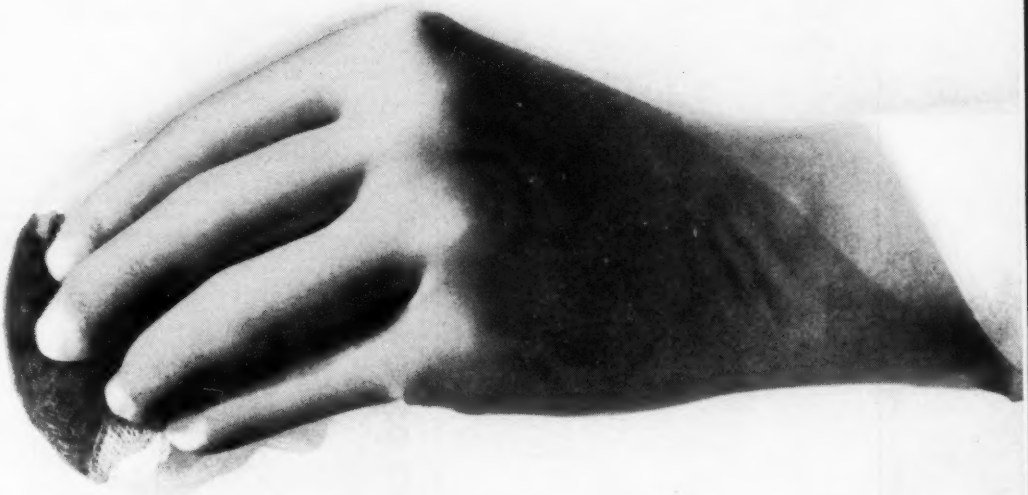

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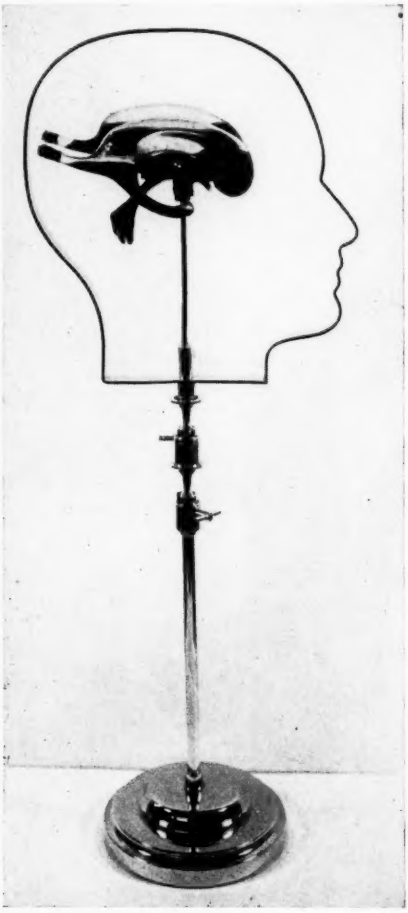

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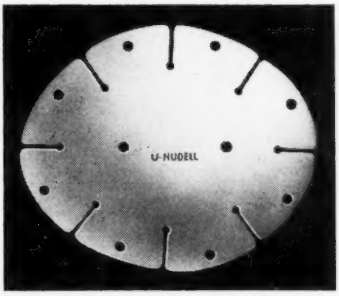

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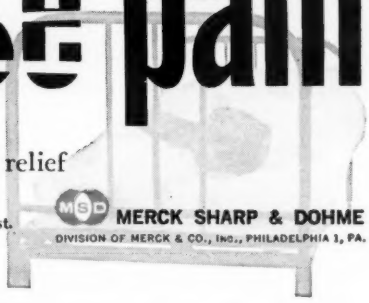

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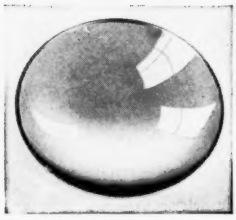

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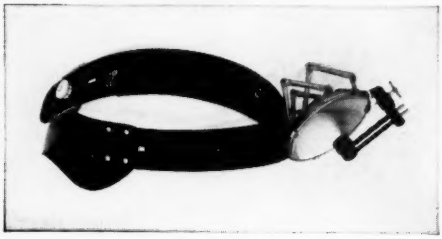

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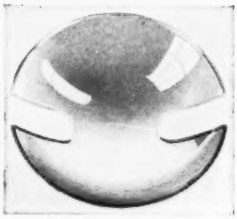

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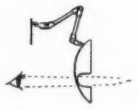

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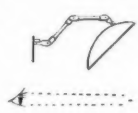

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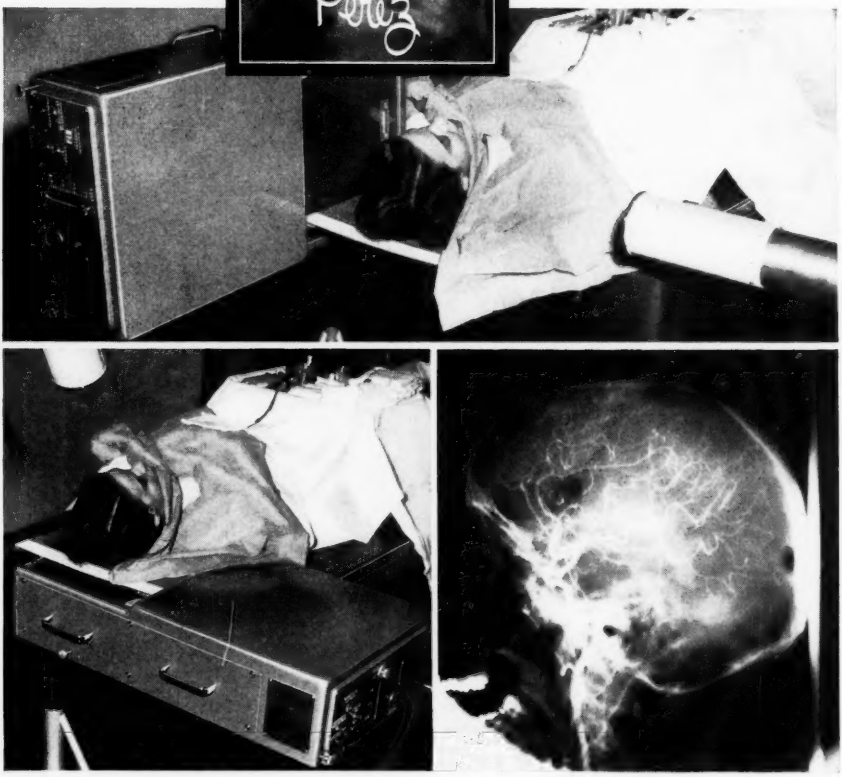

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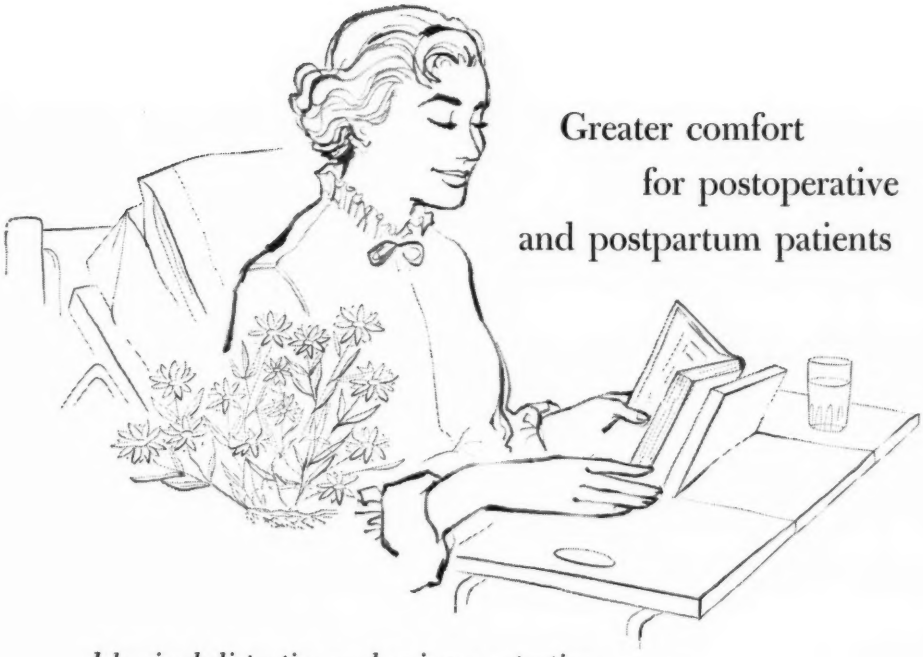

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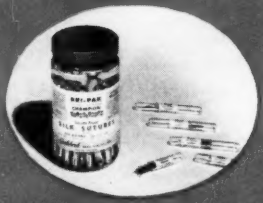

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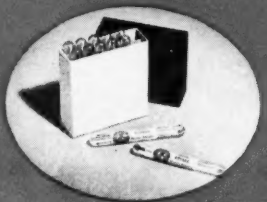

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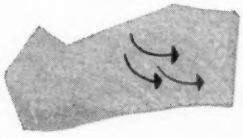

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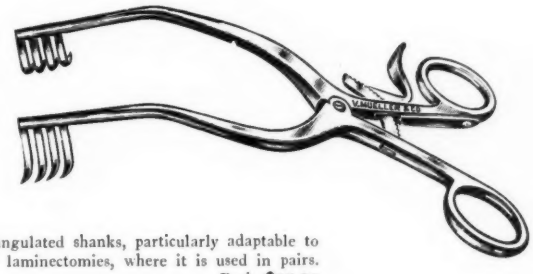

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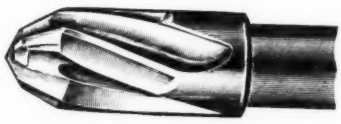

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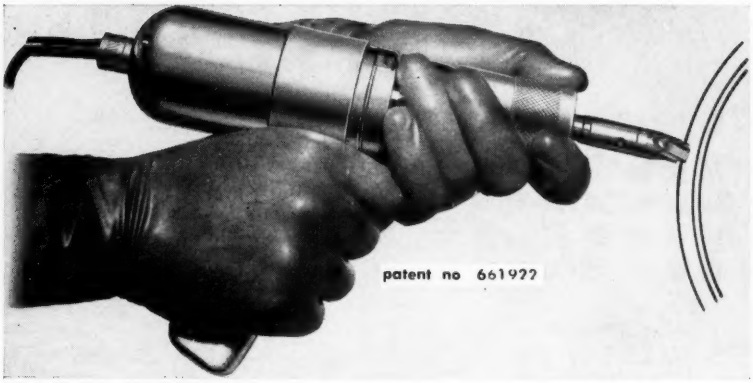

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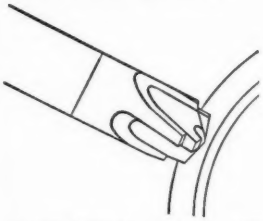

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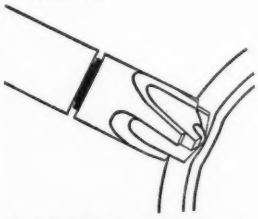

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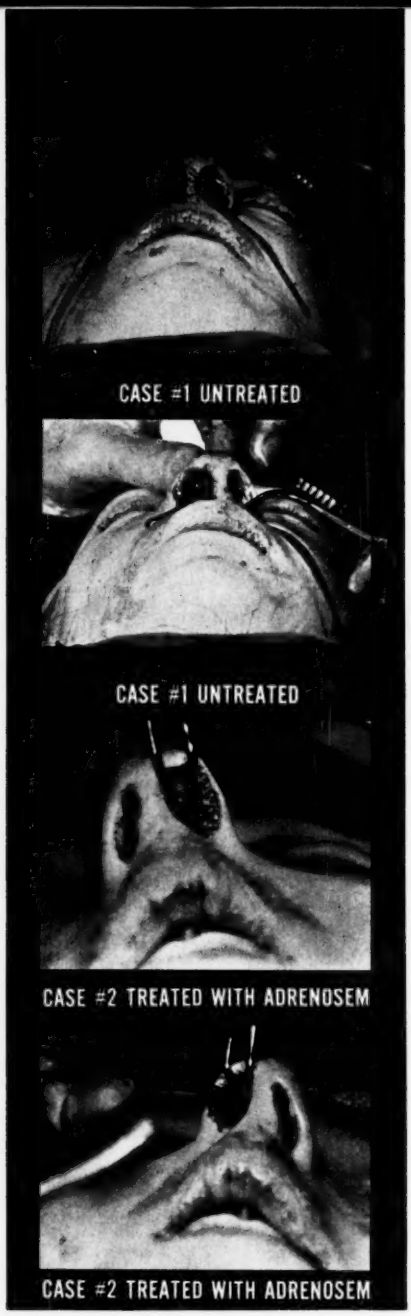

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SIGNS AND SYMPTOMS OF SUPRATENTORIAL ARTERIOVENOUS ANEURYSMS

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(Received for publication June 18, 1957)

IN 1936, in a monograph by Bergstrand, Olivecrona and Tönnis,[1] it was pointed out that the circulatory disturbance in the neighborhood of arteriovenous aneurysms was the probable cause of the clinical signs associated with these lesions. This supposition in the meantime has been confirmed and extended by the gas-analytical methods of Kety and Schmidt, and serial angiographic examinations.

In such vascular anomalies the so-called peripheral portions of the vessels are not in function because arteriovenous fistulas shunt the blood directly into the venous system. Since there is no peripheral vascular resistance in this part of the system, a speedier circulation results within the malformation, and the carotid-jugular blood flow is enlarged without increase in circulation within the brain itself. According to papers of Shenkin *et al.*,[19] Bessman *et al.*,[3] Bernsmeier and Siemons,[2] Gänshirt and Schiefer,[6] and others, gas analysis has proved that there is a circulatory increase up to three to four times the normal blood flow.

However, the value of such gas analysis based on Fick's principle for measuring blood flow in arteriovenous aneurysms may be subject to critique. The blood passing the aneurysm, i.e. the shunt, loses no N_2O to cerebral tissue; consequently in the jugular vein there prevails a mixture of blood from normal vessels of the brain (with reduced N_2O tension) and blood that has passed the arteriovenous aneurysm (with practically unchanged N_2O content). Measuring the difference in arteriovenous N_2O is therefore handicapped, according to the size of the malformation. As the difference in concentration is reversely proportional to the amount of blood flow, greater circulation is accompanied by greater inaccuracy in measuring. Kety and Schmidt's gas-analytical results therefore may be applied to the arteriovenous aneurysms only with certain reservations.

Comparison with serial angiographic findings likewise reveals that the circulatory increase concerns the arteriovenous aneurysm but not the remainder of the brain. Even a reduction in circulation in the area surrounding the aneurysm may be found frequently in the angiograms together with hypertrophy of the arteries leading to the malformation. This may be shown most clearly by comparing angiograms before and after total extirpation of the vascular anomaly: circulation is back to normal and vessels not belonging to the aneurysm, which were invisible before the operation, may

now be seen. Hypertrophy of the supplying vessels has vanished within a short time.

Serial angiography permits measuring the time of circulation within the arteriovenous aneurysm as well as in the brain proper (Table 1). Generally this time is substantially shorter in the aneurysm than in the brain. Certain exceptions may be observed in very large arteriovenous aneurysms. If the cerebral circulation is increased to double the normal amount—then the circulatory difference between brain and arteriovenous aneurysm is reduced to less than a second. The greater length of vascular pathway in these large malformations cannot account for this fact entirely. Probably increased turbulence of the blood causes the slowing up of the flow of the contrast medium. Schurr and Wickbom[18] have published a picture demonstrating such a retardation of the contrast fluid.

In the medium-sized arteriovenous aneurysm (circulatory rates between 105.0 and 62.5 ml./100 g./min.) the difference in the circulatory time between brain and the malformation is 1.8–3.0 seconds. Two patients with obvious lengthening of circulatory time-rate (Table 1) had smaller arteriovenous aneurysms accompanied by large intracerebral hemorrhages, combined with a lowering of cerebral circulation down to subnormal values. This was probably caused by the effect of increased intracranial pressure on vascular portions with low blood-pressure rates, i.e. capillaries and veins. As there is no equivalent to capillaries in the arteriovenous aneurysm and intravenous pressure is increased, an influence of higher intracranial pressure

TABLE 1

Circulation-time and rate of brain circulation in 17 cases of arteriovenous aneurysm

Location of Arteriovenous Aneurysm	Circulation-Time (Seconds) (Serial Angiography)		Cerebral Circulation ml./100 g./min. N_2O Gas Analysis
	Brain	Arteriovenous Aneurysm	
Parietal, lt.	4.8	4.9	239.0
Temporoparietal, rt.	5.8	4.0	180.5
Temporal, lt.	—	4.0	180.0
Frontomedial, rt.	4.7	4.0	163.0
Central, rt.	5.8	4.7	145.0
Parietal, rt.	5.1	4.3	136.0
Frontoparietal, lt.	6.7	4.0	105.0
Parietal, lt.	5.8	4.0	96.0
Precentral, rt.	5.8	4.0	90.3
Occipital, lt.	5.8	4.0	90.0
Occipital, rt.	6.8	4.1	88.1
Temporal, rt.	6.8	3.8	85.0
Side ventricle, rt.	6.8	4.1	84.0
Occipital, lt.	5.8	4.0	72.8
Occipital, lt.	5.6	3.0	62.5
Frontomedial, lt.	8.6	4.9	42.9
Occipital, rt.	12.0	7.0	37.0

on the circulation-rate of the malformation can be expected only exceptionally. Thus in the last case in Table 1 the arteriovenous aneurysm was very small with one arterial influx and long-stretched venous branches. This accounted for the slowing up of circulation within this particular aneurysm.

Although the literature on diagnosis and therapy of vascular malformations has grown considerably within the last two decades, no essentially new facts have been reported on their symptomatology. Moreover, most of the papers are based on only a few personal observations. It might therefore be of interest to compare reports on some of the larger series, details of which are given in Table 2. They show primarily a 2:1 predominance of the male sex. There are no major discrepancies relating to the age of the patients—the malformation manifests itself in the second or third decade of life for the first time. This fact may be of great diagnostic value (Fig. 2).

The predominance of these malformations in the age group between 20 to 40 years appears contradictory to their innate character. We tried to elucidate causes for this relatively late start of clinical manifestations in 1936. Postnatal growth may be one of the roots of this problem.[15,26] Another factor seems to be of greater importance: with the switch over from the infantile to the adult circulation the adaptability of capillaries and smaller arteries decreases. Thus necessary collateral circulation can no longer be maintained on the same scale as before. This causes nutritional disturbances in the neighborhood of arteriovenous aneurysms.

It is a generally accepted view that epileptic fits are the most frequent symptom of the cerebral arteriovenous aneurysm. Of our patients, 53 per cent suffered from epileptic seizures. In addition, in 18 per cent hemorrhage accompanied the epileptic manifestations. Taking into consideration the location of the arteriovenous aneurysm (Table 3) it becomes apparent that

TABLE 2

Distribution of sex and age, and course of illness in reported cases of arteriovenous aneurysm

Author	Year	No. of Cases	Sex		Age Rate (Decades)	Course of Illness			
			Male	Female		Seizures	Hemorrhage	Seizure+Hemorrhage	Other Disturbances
Bergstrand *et al.*[1]	1936	22	15	7	2/3	68%	14%		18%
Jefferson[9]	1948	27	17	10	3	37%	37%		26%
Weber[30]	1948	15	10	5	2/3	27%	27%	40%	6%
Tönnis & Lange-Cosack[25]	1953	72	48	24	2/3	44%	28%		28%
MacKenzie[12]	1953	50	25	25	2	32%	30%		38%
Olivecrona & Ladenheim[14]	1957	125	83	42	2/3	40%	39%		20%
Tönnis	1958	134	88	46	2/3	36%	33%	17%	14%

TABLE 3

Location and course of arteriovenous aneurysms

	frontal	temp. and Sylvian fiss.	centro-parietal	occipital	side ventricle	brain stem and others	cere-bellum	ext. carot. circulation	
subarachnoidal hemorrhage	63%	42%	10%	64%	66%	44%	12.5%		40
mixed seizures+hemorrhage									21
seizures									45
palsy									6
other symptoms									22
	16	26	50	11	3	9	8	11	134

epileptic seizures characterize chiefly centrally and precentrally located arteriovenous aneurysms, but may rarely be found in anamneses of patients with malformations in a frontal or occipital location. Jacksonian seizures are found mainly in cases of central lesions. In 2 patients with temporal vascular malformations, psychomotor fits with oral manifestations could be observed. A patient with an occipital aneurysm noted paroxysmal hallucinatory visions. Between the epileptic group and the patients suffering from hemorrhage differences of age grouping cannot be found (Fig. 1).

All of papers of the last two decades demonstrate a high interest in intracranial hemorrhage (subarachnoidal or intracerebral), especially after it had become known that hemorrhages are caused frequently by malformations that may be treated surgically.[5,7,8,13,20–24,28,29] Out of 112 patients with supratentorial arteriovenous aneurysms, 40 (i.e., 36 per cent) showed the syndrome of subarachnoidal hemorrhage only; a further 21 (i.e. 18 per cent) had hemorrhage and seizures as well. Recently, however, the observations of hemorrhages have increased, now reaching down to even the first 10 years of life—in contrast to former observations.

If subarachnoidal hemorrhage occurs, differential diagnosis must consider an arteriovenous aneurysm, a saccular aneurysm, hemorrhage into a brain tumor or a so-called spontaneous intracerebral hemorrhage. This last group probably comprises very small arteriovenous or saccular aneurysms of the cerebral vascular periphery, which rupture and are closed by subsequent thrombosis respectively. This may account for the failure to find them post mortem. Their prevalence in relation to age corroborates this assumption (Fig. 2). All other causes of subarachnoidal hemorrhage are of less importance. Only after exclusion of the aforementioned causes may one consider

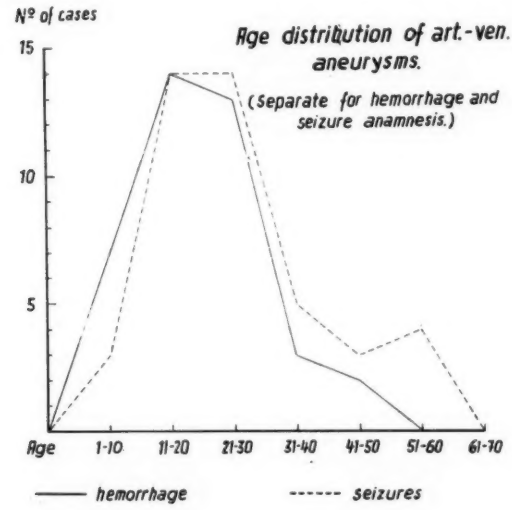

FIG. 1. Ages of patients in relation to hemorrhage and seizures.

the rare sources such as certain infectious disorders, diseases of the blood (for instance hemolytic jaundice), avitaminosis, toxic states, etc. But numerically these are quite unimportant. With senescence hemorrhage caused by arteriosclerotic impairment of the blood vessels of the brain reaches special importance.

The decision as to what therapeutic steps should be taken depends in general on the angiographic localization of the source of the hemorrhage.

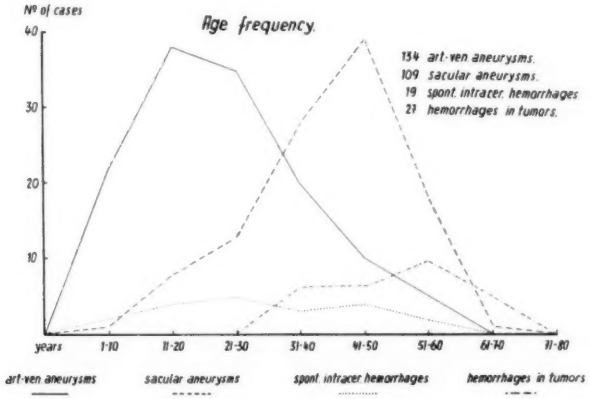

FIG. 2. Frequency of arteriovenous aneurysms, saccular aneurysms, spontaneous hemorrhage and hemorrhage in tumor, in relation to age.

Differential diagnosis for the neurosurgeon may be supported by mere observation of the *temporal course* and *clinical signs* of the ailment.

The following diagnostic suggestions are based upon observation of 134 arteriovenous aneurysms, 109 saccular aneurysms, 19 spontaneous intracerebral hemorrhages, as well as 27 cases of hemorrhage in brain tumor.[27]

It was found that arteriovenous aneurysms prevail chiefly in younger individuals. Saccular aneurysms are most frequent in those between 45 and 50 years of age. Spontaneous hemorrhage occurs mostly in patients of medium age, whereas those of the tumor group reach later ages (Fig. 2).

The predominance of arteriovenous aneurysms in males has already been mentioned. The distribution of sex in cases of spontaneous hemorrhage is quite similar. In the group of saccular aneurysms such discrepancies in sex are not shown.

The question as to whether bodily or psychic strain may cause *subarachnoidal hemorrhage* is generally answered in a negative way.[4,10,13,17] Our material, however, does not permit exclusion of these influential factors—even if the causality-minded patient's story is taken into consideration. Whereas in cases of arteriovenous aneurysms these extrinsic causes are of minor importance, some reservation may perhaps be made with regard to saccular aneurysms (exogenous causes having been accused in 27 per cent of hemorrhages from arteriovenous aneurysms, but in 65 per cent of hemorrhages from saccular aneurysms).

Length of unconsciousness gives no hint, but *neurologic symptoms*, especially pathology of cranial nerves, appear to be more frequent in patients with saccular aneurysms. Thus we did not find neurologic symptoms in 51 per cent of the cases of arteriovenous aneurysms; in 34 per cent there were transient, and in only 15 per cent fixed neurologic signs. On the other hand, neurological symptoms persisted in 36 per cent of the cases of saccular aneurysms and in two-thirds of the cases of spontaneous hemorrhage. Comparison of the *kind of symptoms* in patients with arteriovenous aneurysms and those with saccular aneurysms shows that in the former group 7 per cent had involvement of the cranial nerves, in contrast to 47 per cent in the latter group.

Patients with spontaneous hemorrhage and those with hemorrhage in brain tumors do not show such involvement of cranial nerves. Impairment of consciousness, and vegetative disturbances with their effect on the general physical condition, disappeared in 60 per cent of patients suffering from an arteriovenous aneurysm even after a second or third hemorrhage, allowing fast recuperation of the patients. After a hemorrhage in a saccular aneurysm, improvement begins in 40 per cent of the cases only after 4 weeks or later. *Thus hemorrhage in saccular aneurysms generally produces a much graver picture than in arteriovenous aneurysms.* As a matter of fact, the cure of hemorrhage in tumor takes even longer, if an improvement comes about at all: the further course depends mainly on the progression of the brain-tumor symptoms.

Several subsequent hemorrhages may take place in arteriovenous aneurysms (in 36 per cent) as well as in saccular aneurysms (in 46 per cent), whereas in patients with spontaneous hemorrhage or with hemorrhage in tumors the prognosis is contingent on increasing intracranial pressure. Taking into consideration the *time between several hemorrhages*, most of the arteriovenous type show intervals of several years (longest interval between 2 episodes of hemorrhage: 28 years). Saccular aneurysms, on the other hand, often show a fast sequence of hemorrhages (Fig. 3). Possibly this difference is ascribable to higher intravascular pressure and faster blood flow in the large arteries, preventing exsanguination by thrombosis.

Thus mere observation of the course and of the clinical symptoms accompanying cerebral hemorrhage can give essential hints towards a specific diagnosis of its cause. A detailed description of neurological symptoms in relation to different locations of arteriovenous aneurysms would lead to considerable advance, especially since new facts have not been brought out.

However, *chronic psychiatric disorders* are of greater interest. There have been statements to the effect that psychic changes become graver the more frontally an arteriovenous aneurysm is located. Yet, Riechert and Zillig[16] in 1940, and others, warned against basing localization on psychopathology.

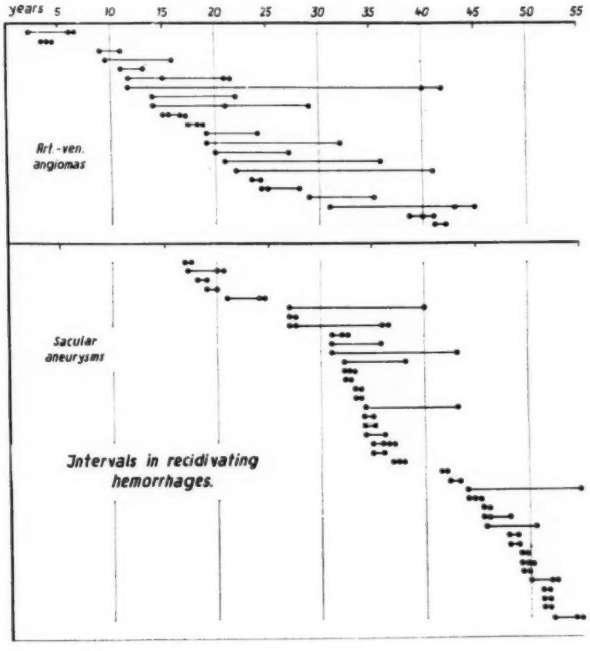

FIG. 3. Time intervals in recidivous hemorrhages.

Lange-Cosack[11] has examined the psychiatric impairments in 76 cases of our material. Table 4 shows that *psycho-organic deficiency* has an over-all importance. Epileptic behavioral changes were found in 3 cases only. Table 4 demonstrates, moreover, that the degree of psychiatric disorders depends on the size of the arteriovenous aneurysm and the intracranial pressure (hemorrhages) only, and not on the location of the malformation. The more diffuse and extensive the malformation, the stronger are the effects of cerebral circulatory deficiency and subsequent atrophy of the brain. We are in agreement with Olivecrona and Riives[15] in considering the latter as causing the progressive mental deterioration.

Finally *electroencephalographic changes* associated with such malformations may be mentioned. There is an intimate relation between elec-

TABLE 4

Chronicpsychiatric disorders and size of arteriovenous aneurysm

Size of Arteriovenous Aneurysm	Chronic Impairment of Consciousness	Affective Changes	Organic Cerebral Deficiency	Personality Changes with Dementia	Epileptic Personality Behavior	Organic Personality Change	No. with Psychiatric Disorders	Total No.
Small and medium	—	1	11	—	—	1	13	27
Large	1	3	18	1	3	2	28	34
Diffuse	1	2	4	4	—	—	11	11
Extracranial (external carotid artery)	—	1	2	—	—	—	3	4
Total	2	7	35	5	3	3	55	76

trical brain phenomena and the consequences of the hemorrhage. Moreover, paroxysmal activity may be found in patients with seizures. Of 58 electroencephalographic recordings, pathological phenomena were present in 78 per cent (i.e. 14 per cent, a general disorder and 64 per cent, focal activity). As a rule, the more recent the hemorrhage, the greater is the incidence of focal disturbances. Up to the 8th week after its occurrence a focal-wave activity and bilateral paroxysmal activity are the main features. Afterwards — waves and — wave reduction mark the focal patterns. Twenty per cent of the patients had actual epilepsy potentials apart from the local slowing down of electrical activity. But only in 50 per cent of patients with clinical seizures could such epileptic electroencephalographic potentials be recorded. One remarkable observation should be reported: 3 children between 10 and 12 years of age had epileptic electroencephalographic potentials without clinical manifestations of seizures.

There is no clear-cut relation between the size of the malformation and the extent of electroencephalographic pathology. In the cases of arteriovenous aneurysm with influx from merely the external carotid artery the electroencephalographic activity was normal in our material.

There can be no doubt that the final diagnostic decision in a case of arteriovenous aneurysm will always depend on cerebral angiography. But the above-stated facts show that careful study of the course of the disease and of the clinical findings may tend to essentially clear up any such case.

SUMMARY

A report on a larger series (134 cases) of arteriovenous aneurysms is presented. The material is compared with that in similar papers in the literature. Special attention is given to the evaluation of purely clinical symptoms, allowing a specific diagnosis without the primary help of more complicated diagnostic techniques. The evaluation of the age, temporal intervals between the hemorrhages, and the extent of neurological signs as well as the importance of psychiatric disorders are stressed. Serial angiographic findings corroborated by gas-analytical examinations may elucidate the pathophysiological mechanism of arteriovenous malformations. Electroencephalographic findings associated with arteriovenous aneurysms are considered.

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PITUICYTOMA. TUMOR OF THE SELLA TURCICA

A CLINICOPATHOLOGICAL STUDY*

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(Received for publication July 22, 1957)

THE cellular elements of the neurohypophysis are modified glial elements. Their specific morphological characteristics were recognized by Bucy,[1] who named them pituicytes. The pituicytes can be divided into four groups:[5] (1) bipolar, (2) astrocyte-like, (3) triangular, and (4) glomerular. The cells of the first group (the bipolar pituicytes) have elongated or oval bodies and their protoplasm may be either homogeneous (group 1A), or granular (group 1B). The pituicytes are capable of producing tumors (pituicytomas) which are formed either by several of the above-named groups of pituicytes[6] or by one of the groups. The latter type of pituicytoma is the subject of the present study.

CASE HISTORY

R.E.B., a 47-year-old white female, was first seen at the University Hospital in August 1947 with a chief complaint of diminution in vision. This had been noted progressively over the past 5 years. Past history revealed that menstruation had ceased spontaneously 12 years before at the age of 35. In 1942 the patient began to notice decreased libido, increased intake of fluids and almost complete loss of body hair.

Examination by the Department of Ophthalmology revealed bilateral primary optic atrophy. The vision was 6/30 OD and 6/15 OS. Visual fields revealed a suggestion of a bitemporal hemianopsia most marked in the upper quadrant OD.

Roentgenograms of the skull showed intrasellar erosion and hyperostosis of the inner table of the frontal and parietal bones.

Course. Roentgen-ray therapy was started August 1947 and the patient received a total of 2100 r to left and right pituitary fields. There was no appreciable skin reaction at the end of this time.

The vision continued to deteriorate over the next $3\frac{1}{2}$ months and on Nov. 20, 1947, the bitemporal hemianopsia was complete. The visual acuity at this time was 5/60 OD and 5/9 OS.

1st Operation. On Nov. 21, 1947 a large intrasellar tumor was disclosed. The tumor was unusually adherent to both optic nerves and the chiasm. These structures were thoroughly decompressed.

Histological identification of the tissue removed was not possible.

Course. There was never any evidence postoperatively of diabetes insipidus. Specific gravity of the urine was 1.011. Sugar was never found in the urine. Some

* Supported by grant from United States Department of Health, Education and Welfare, B-1251.

improvement in vision was noted over the next few months and the patient returned to her housework. Her vision was sufficient to permit driving a car.

She was seen again on Feb. 14, 1957. She had had a sudden and rapid decrease in vision over the past 12 days. Visual fields revealed marked concentric contraction of both nasal fields with complete bitemporal hemianopsia. Visual acuity was 22/100 OD and 21/100 OS. Marked optic atrophy was present.

2nd Operation. The patient was prepared with cortisone and an operation was performed the following day. A large intrasellar tumor was present, markedly compressing the right optic nerve and chiasm. On excising the capsule, reddish purplish tumor was seen. It was believed that hemorrhage had taken place into the tumor. The tumor was exceedingly firm in consistency and could be removed only by sharp dissection. It was estimated that the diameter of the tumor was 2.0 cm.

Course. The patient was exceedingly drowsy immediately after operation, but was awake and oriented 1 week later. There was no evidence of diabetes insipidus and 7 days postoperatively the specific gravity of the urine was 1.025. She was receiving cortisone at this time, but no pituitrin. Sugar was never present in the urine. The patient lapsed back into coma, responding only to painful stimuli. In spite of all types of supportive therapy, including intravenous hydrocortisone, she died March 14, 1957.

Autopsy. The brain weighed 1250 gm. There was an area of softening in the posterior aspect of the right frontal lobe which included the hypothalamus and infundibulum and reached the mammillary bodies. The right frontal lobe was congested. A silver clip was present on the right anterior cerebral artery $1\frac{1}{2}$ cm. anterior to the anterior communicating artery. Several clips were also present over the margin of the diaphragma sellae. The dorsum sellae was soft. The posterior part of the sella turcica was filled by a firm tumor mass about 2 cm. in diameter.

The upper half of the right kidney was replaced by a mass $7 \times 7\frac{1}{2} \times 3\frac{1}{2}$ cm. in diameter. This mass was well encapsulated and did not extend into the renal vascular system. Histologically this neoplasm was classified as hypernephroid carcinoma.

In the lungs were found mucopurulent bronchitis and early pneumonia.

Methods. The tumor from the sella turcica was removed in toto with the sella and part of it was embedded in paraffin and stained with hematoxylin and eosin, phosphotungstic-acid hematoxylin, chrome-hematoxylin-phloxin, aldehyde-fuchsin, trichrome and other methods.

The remaining part of the tumor was removed from the sella, fixed in bromformalin (Cajal's solution) and was impregnated by silver carbonate techniques of del Río-Hortega[7,8] and their modifications.[4]

Description of Material. The neoplasm in the sella turcica occupies the posterior lobe of the neurohypophysis. The anterior lobe is compressed but not invaded (Fig. 1). The tumor is formed by masses of large cells which are arranged in groups. The cytoplasm of these cells is finely granular and Gomori-negative. The majority of the cells are large in size and no mitotic figures are present. Some of the cells are elongated and bipolar (Fig. 2); other elements are large, and oval in shape with indistinct cellular boundaries (Fig. 3). With silver impregnation the granules in the cytoplasm and the long straight processes stand out clearly (Fig. 4). There are also cells with elongated bodies, poorly defined cellular outlines and thick, coarse processes (Fig. 5). The neoplastic elements form syncytium-like structures in which the large nuclei stand out clearly but the cell bodies can be recognized only by the accumulation of

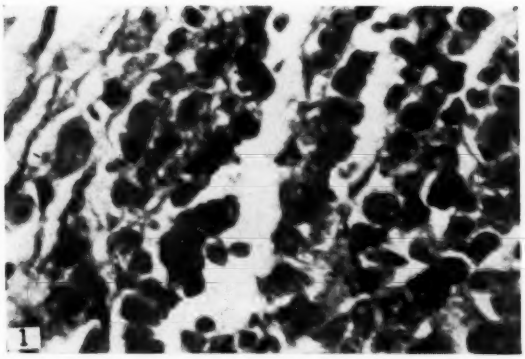


FIG. 1. Pituicytoma. Cells of anterior lobe of hypophysis. Chrome-hematoxylin-phloxin, 40×.

the granules (Fig. 6). Some of these cells are very large and almost round in shape (Fig. 7).

These blastomatous elements can be identified as the bipolar type of pituicytes with granules in the cytoplasm (group 1B). Fig. 8 shows a bipolar pituicyte from a normal human neurohypophysis. Normally the bodies of these cells are spindle-shaped or elongated and have two straight processes. This type of pituicytes can be easily distinguished from the bipolar pituicytes of group 1A, since the latter variety has a homogeneously impregnated cytoplasm and two polar wavy processes (Fig. 9).

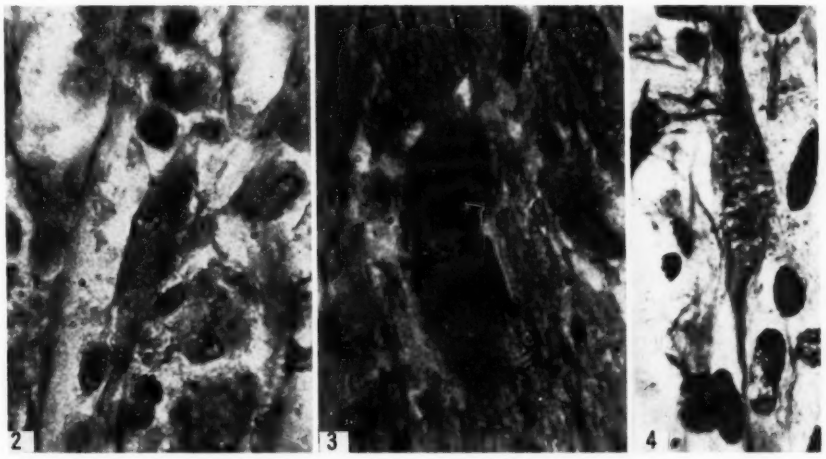
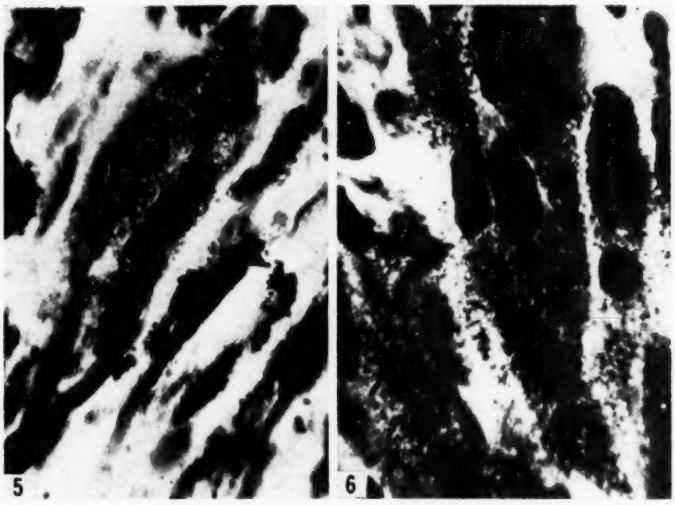


FIG. 2. Pituicytoma. Blastomatous pituicyte with elongated cell body. Chrome-hematoxylin-phloxin, 100×.

FIG. 3. Pituicytoma. Neoplastic element with large oval cell body. Chrome-hematoxylin-phloxin, 100×.

FIG. 4. Pituicytoma. Spindle-shaped blastomatous pituicyte with two polar processes. Silver carbonate, 100×.



FIGS. 5–6. Pituicytoma. Groups of tumor cells. Protoplasm is filled with granules, and cell boundaries are indistinct. Silver carbonate, 100×.

In normal neurohypophyses the bipolar pituicytes with granular cytoplasm are found only occasionally among other types of pituitcytes (Fig. 10). These protoplasmatic granules are Gomori-negative (Fig. 11). Figs. 12–14 show different types of normal pituicytes of group 1B. The pituicyte in Fig. 12 is spindle-shaped, the granules are very dense and the nucleus of the cell is not distinguishable. Other elements of this type have large nuclei, granules in the cytoplasm and two wavy processes, one of which is shown in Fig. 13. Some of the pituicytes may have an almost round cell body and eccentric nucleus (Fig. 14).

FIG. 7. Pituicytoma. Round blastomatous pituicyte. Silver carbonate, 100×.

In the pituicytoma are found different cellular forms which represent blastomatous forms of group 1B. Among the typical large cells with granulated cytoplasm are present some with palely impregnated cytoplasm and indistinct granules (Fig. 15). There are also cells with a very dense accumulation of granules; these cells appear almost homogeneously impregnated (Fig. 16). Another variation of the blastomatous pituicytes is represented by small cells with one visible thick process which is also filled with the coarse granules (Fig. 17). Normal-appearing pituicytes are also found in small numbers in the area of the tumor. Fig. 18 shows groups of

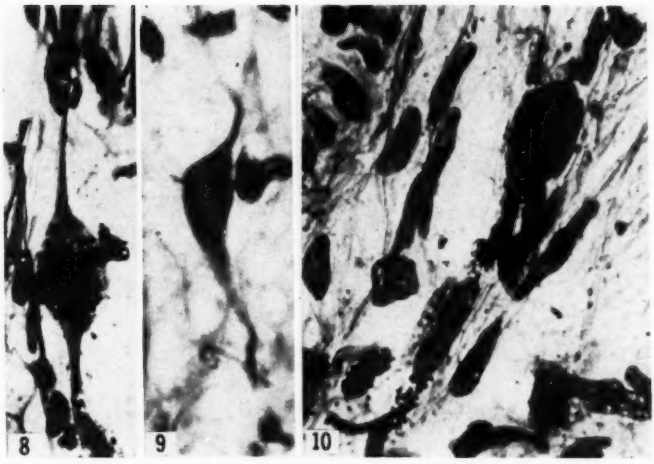


FIG. 8. Normal neurohypophysis. Typical bipolar pituicyte (group 1B) with spindle-shaped body, large nucleus, granules in protoplasm and two straight processes. Silver carbonate, 100×.

FIG. 9. Normal neurohypophysis. Typical bipolar pituicyte (group 1A) with homogeneously dark impregnated protoplasm and two wavy processes. Silver carbonate, 100×.

FIG. 10. Normal neurohypophysis. Large pituicyte (group 1B) with protoplasm and process filled with granules. Silver carbonate, 100×.

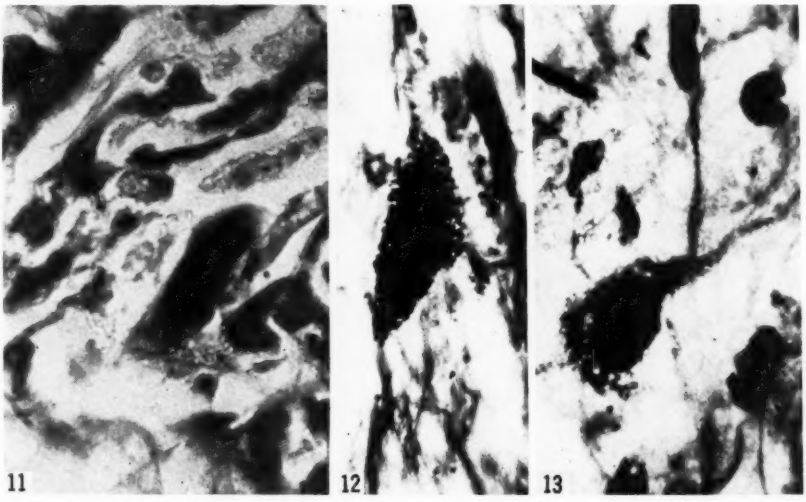


FIG. 11. Normal neurohypophysis. Bipolar pituicyte filled with Gomori-negative granules. Chrome-hematoxylin-phloxin, 100×.

FIG. 12. Normal neurohypophysis. Pituicyte (group 1B), with spindle-shaped body and very numerous granules in the protoplasm. Silver carbonate, 100×.

FIG. 13. Normal neurohypophysis. Pituicyte (group 1B) with a large nucleus and sparse protoplasm filled with coarse granules. Silver carbonate, 100×.

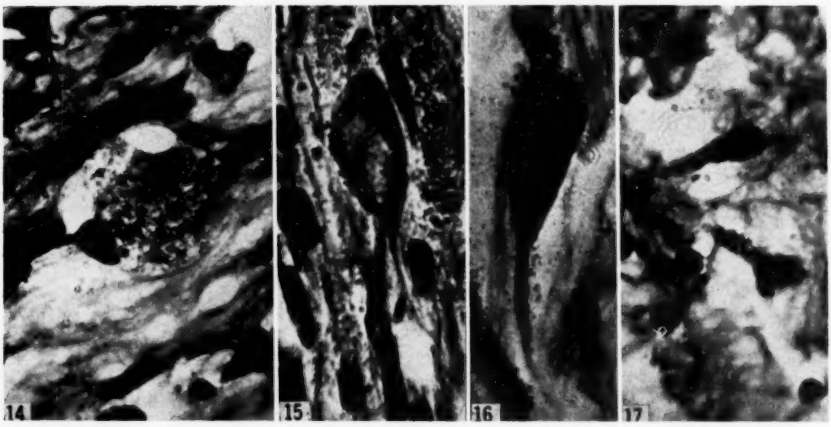


FIG. 14. Normal neurohypophysis. Pituicyte (group 1B) with eccentric nucleus and round cell body filled with fine granules. Silver carbonate, 100×.

FIG. 15. Pituicytoma. Blastomatous pituicyte with pale cytoplasm and one impregnated process. Silver carbonate, 100×.

FIG. 16. Pituicytoma. Blastomatous pituicyte. Very dense accumulation of granules gives this cell a homogeneous appearance. Silver carbonate, 100×.

FIG. 17. Pituicytoma. Blastomatous pituicytes of small variety. The cell bodies and the thick processes are filled with coarse granules. Silver carbonate, 100×.

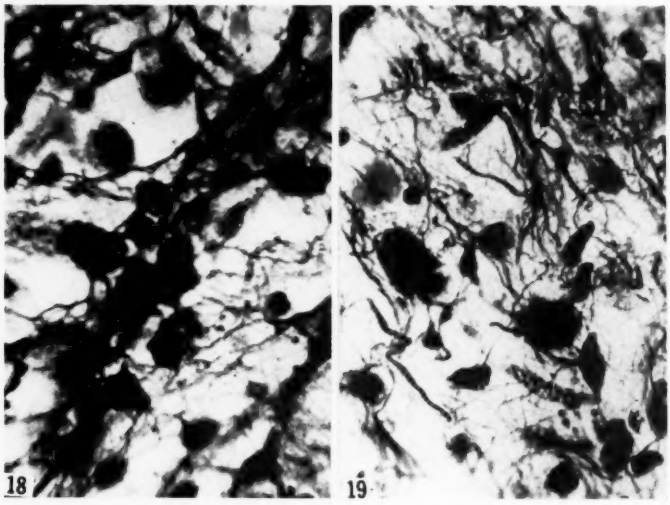


FIG. 18. Pituicytoma. Astrocyte-like pituicytes (group 2). Silver carbonate, 100×.

FIG. 19. Normal neurohypophysis. Astrocyte-like pituicytes (group 2). Silver carbonate, 100×

astrocyte-like pituicytes (group 2). These cells appear normal and are identical with the pituicytes of the same variety found in normal neurohypophyses (Fig. 19). In the pituicytoma were also found bi- and unipolar cells with oval cell bodies, which are homogeneously impregnated and have long wavy processes (group 1A), as shown in Figs. 20 and 21. Isolated Herring bodies were also found in the tumor tissue (Fig. 22).

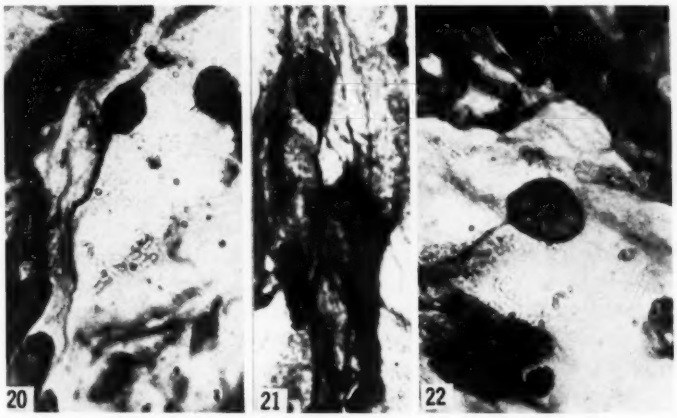


FIG. 20. Pituicytoma. Pituicyte (group 1A) with round cell body and one distinctly impregnated wavy process. Silver carbonate, 100×.

FIG. 21. Pituicytoma. Pituicyte (group 1A) with oval cell body and one impregnated process. Silver carbonate, 100×.

FIG. 22. Pituicytoma. Herring body. Silver carbonate, 100×.

DISCUSSION

The clinical history indicates a neoplasm of 18 'years' duration which caused primarily endocrine disturbances (amenorrhea, transient diabetes insipidus, decreased libido and loss of body hair). The symptoms of diabetes insipidus disappeared spontaneously since there were no signs of it on first and second admissions. In the last 10 years there was loss of vision and erosion of the sella turcica caused by growth of the neoplasm.

A complete histological examination in this case would have required a detailed analysis of the hypothalamic nuclei and infundibulum, but unfortunately these structures were completely destroyed by antemortem softening.

The histological characteristics of the tumor are those of a benign neoplasm. The neoplastic elements show to a certain extent variation in size. They have spindle-shaped or oval cell bodies with protoplasm filled with fine or coarse granules. These cells bear close resemblance to the bipolar pituicytes with granular cytoplasm (group 1B) which are found in normal neurohypophyses in small numbers. As far as examination of the contents of the sella turcica can be determined this neoplasm displays no tendency

toward infiltrating growth, since the anterior lobe was found compressed and without evidence of blastomatous elements. Among the neoplastic elements were found bipolar pituicytes with homogeneously dark impregnated cytoplasm (group 1A) and astrocyte-like pituicytes (group 2). These types of pituicytes appear normal and do not take part in the formation of the tumor. They represent a remnant of normal neurohypophysis which gradually became filled with blastomatous elements of group 1B.

These histological features indicate that in the present case we are dealing with a primary, slow-growing neoplasm which originated in the posterior lobe of the sella turcica. Since the blastomatous elements can be identified as pituicytes, this neoplasm should be classified as a pituicytoma.

Kernohan and Sayre[3] in their recent monograph list the "granular-cell myoblastoma" described by Harland[2] as one of the primary neurohypophysial tumors. This tumor of the neurohypophysial stalk is very similar, if not identical, to the neoplasm described in the present case. Although we feel that there are some histological similarities between the tumors described elsewhere in the body as "granular-cell myoblastoma" and primary tumors arising in the neurophypophysis, the term "granular-cell myoblastoma" should not be applied to a neoplasm that is probably of neuroglial origin.

SUMMARY

A primary tumor of the posterior lobe of the hypophysis was present over an 18-year period. This tumor was formed by pituicytes and should be classified as a pituicytoma.

We would like to express our gratitude to Dr. James French, Chairman of the Department of Pathology, who kindly released for our use the contents of the protocol of the postmortem examination.

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GLIOBLASTOMA MULTIFORME

REVIEW OF 219 CASES WITH REGARD TO NATURAL HISTORY, PATHOLOGY, DIAGNOSTIC METHODS, AND TREATMENT

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(Received for publication July 30, 1957)

IT IS a curious fact that our current neurosurgical literature exhibits a striking paucity of articles about our greatest problem: glioblastoma multiforme.[1,4–10] While the contemporary literature on cancer swells to an overabundance, our "cancer" of the nervous system appears to receive scant attention—certainly not through complacency. Since communication is a leaven of ideas, the present one is offered with that intent. Harvey Cushing continuously recorded his experiences with various types of intracranial tumors, culminating in the great meningioma monograph, with Louise Eisenhardt.[3] In the preface to his *Intracranial Tumours*[2] he stated, "The laying bare of one's mere mortality percentages, however, is only a start toward what will ultimately be called for: namely, figures relating to the expectancy of life of those who have survived tumor extirpations. And still more important would be figures for each kind of tumor which would show the percentage of surviving patients whose wage-earning capacity has been restored by operation and for how long a time." It is for this purpose that this study was undertaken.

MATERIAL

The 219 cases collected here comprise all the verified cases of glioblastoma multiforme seen at the New Haven Hospital during the period 1924–1952. The microscopic sections were reviewed and the diagnosis was verified. A number of doubtful cases were discarded. We are grateful for the valuable assistance of Dr. Louise Eisenhardt and Dr. Elias Manuelidis in reviewing the microscopic sections when the diagnosis was questionable.

Aside from histological verification, the cases are not selected in any sense. Some of the patients were never seen by a neurosurgeon. Those who came to operation were treated by many different surgeons, many of them residents. The time span represents an entire generation during which many surgical advances came into being, including the blood bank, fluid replacement in its modern sense, and antibiotics.

The follow-up is complete on all of these patients. All have died. Autopsies were done on 105 of the 219, and the findings are known in all but 1 case, in which the autopsy was performed at another hospital.

METHOD

For this statistical survey the hospital charts, microscopic sections, autopsy protocols, and records of the hospital Tumor Registry were used as sources of information. Using a code suitable for transferring the information to IBM punch cards, 50 different items were recorded.* The cards were run through an IBM card counting sorter, permitting computation and correlation of various factors.

AGE INCIDENCE

The age at onset of symptoms is presented in Fig. 1. Two-thirds of the patients were in the fifth and sixth decades. The youngest was 12 years old, and the oldest 73. There were only 2 patients below the age of 20, and 2 over 70.

SEX INCIDENCE

The present series consists of 127 males, or 58 per cent, and 92 females, or 42 per cent. This difference suggests that there might be something in the female endocrine makeup which serves as protection against the occurrence of this tumor. If this were the case, one would suppose that the incidence of glioblastoma might be particularly low in the group of females with actively functioning ovaries.

To examine this question the state of ovarian function was tabulated in the 73 cases of females in which this information was available. None of these patients was prepubertal, 39 per cent were in the reproductive period, while 60.3 per cent were menopausal or postmenopausal. However, in the third and fourth decades, corresponding to the reproductive period, the incidence was greater in females than in males. Also, the peak incidence for both sexes is in the fifth and sixth decades, which corresponds to the menopausal or postmenopausal period of females (Fig. 1). The evidence fails to support a significant correlation between the state of ovarian function and the incidence of glioblastoma.

TOTAL DURATION OF DISEASE

The survival curve is seen in Fig. 2. Total duration is defined as the time from the appearance of the first symptom until death. At the end of 7 months, 50 per cent of the patients were dead while 67 per cent failed to survive 1 year. Another 22 per cent died during the second year. The remaining 11 per cent lived for periods of 2 to 5 years.

The age of the patient seems to have little effect on the duration. When divided into 3 groups consisting of those under 30, those from 30 to 49, and those 50 and over, the survival curves for the 3 groups are not strikingly different (Fig. 3). The course of the oldest group is slightly more rapid, perhaps a reflection of the fact that these older patients are poorer surgical

* Acknowledgment is made to Dr. Edward M. Cohart of the Department of Public Health, Yale University, for his advice in preparing the code.

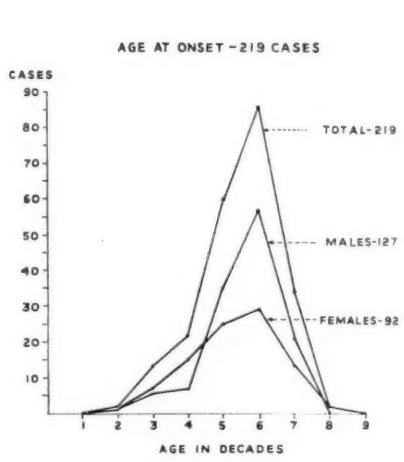

FIG. 1.

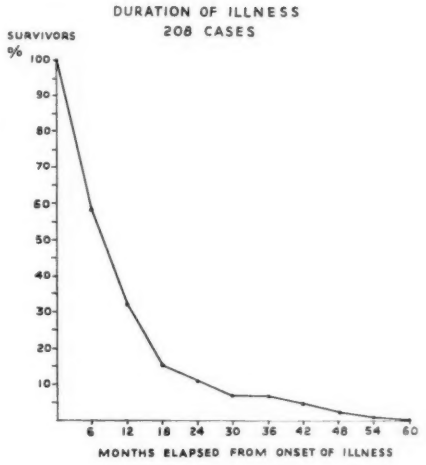

FIG. 2.

risks. In any event, the disease does not run a more rapid course in younger patients, as is often the case with some other neoplasms.

The survival curves of the male and female groups are almost identical. Among the females, there is no significant difference between the survival rates of the reproductive group and the menopausal-postmenopausal group.

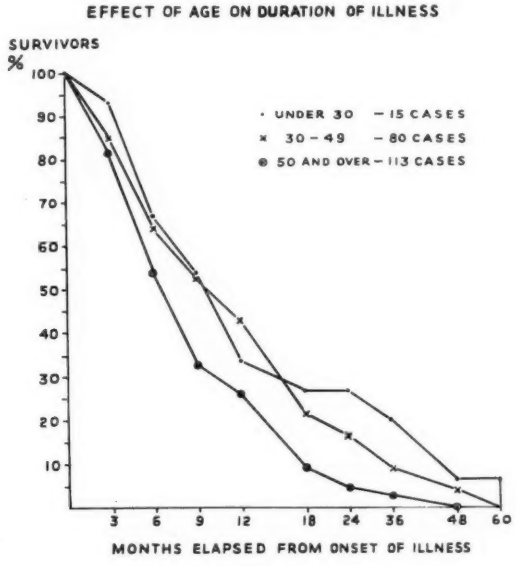
EFFECT OF AGE ON DURATION OF ILLNESS
SURVIVORS
%
· UNDER 30 — 15 CASES
× 30 - 49 — 80 CASES
⊕ 50 AND OVER — 113 CASES
MONTHS ELAPSED FROM ONSET OF ILLNESS

FIG. 3.

DURATION OF SYMPTOMS

The duration of symptoms prior to the time of diagnosis was usually rather brief. The duration was less than 6 months in 70 per cent of the patients, while 83 per cent had a history of less than 1 year. It is worth noting, however, that 17 per cent in this series had histories of over a year's duration: 10 per cent between 1 and 2 years, and the remainder from 2 to 5 years. The patient with the longest history was a 28-year-old woman who was admitted in extremis, 7 months pregnant, with a 5-year history of generalized seizures. She died before treatment could be instituted.

SYMPTOMATOLOGY

It is well known that the symptomatic onset of glioblastoma multiforme may be extremely abrupt, simulating a vascular accident. This type of apoplectic onset was noted in only 8 of these patients. In 2 cases the mode of onset is not known, while in the remainder it was gradual.

TABLE 1

Symptomatology

	Present (Per Cent)	Initial Symptom (Per Cent)	Chief Complaint (Per Cent)
Headache	86	37	35
Mental change	47	7	3
Nausea, vomiting	45	0	1
Motor	44	3	5
Visual	39	5	2
Altered consciousness	39	3	7
Gait disturbance	35	2	0
Cranial nerve*	35	4	1
Personality change	34	7	1
Seizures	32	16	10
Aphasia	32	5	4
Sensory	23	4	1

* Not including optic nerve.

The symptoms complained of are listed in Table 1, with data also on the frequency with which each was the initial symptom and the chief complaint. Headache is the leading symptom by a wide margin in all 3 categories. Approximately a third of the patients had seizures and in half of these it was the initial complaint.

FAMILIAL INCIDENCE

Of 163 cases in which a family history was recorded, only 3 were positive for brain tumor. The type of tumor is not known in any of these.

COINCIDENCE WITH OTHER NEUROLOGICAL DISEASE

The history of each of these patients was examined to see whether glioblastoma multiforme tends to be associated with any other neurological

disease. The following associations were noted: 1 patient had von Recklinghausen's disease; 17 gave a past history of head injury; 9 had various psychiatric diseases, including 1 with mental deficiency; 2 had epidemic encephalitis, 1 having Parkinsonism as a sequel, the other seizures; 1 case each of the following: chorea plus a "stroke," migraine, Bell's palsy, meningitis. There is nothing to suggest that any of these were more than chance associations.

INCORRECT DIAGNOSIS

An initial diagnosis other than brain tumor was made in 25 instances as follows: 7 cases were initially diagnosed as cerebral thrombosis; 3 were thought to be psychiatric problems; 4 were labeled epilepsy; 3 patients were thought to have subdural hematoma, and another a subcortical hemorrhagic cyst of traumatic origin—a diagnosis made at the operating table; 2 patients were thought to have encephalitis. The following erroneous diagnoses were made once each: alcoholic neuritis, Sydenham's chorea with Bell's palsy, poliomyelitis, paresis, porencephaly, and "chronic progressive encephalopathy."

In 5 instances a brain tumor other than glioblastoma was diagnosed: 3 astrocytomas, 1 meningioma, and 1 metastatic tumor.

DIAGNOSIS

It is of interest to inquire into the usefulness of various diagnostic studies performed on patients suspected of having a brain tumor.

Lumbar Puncture. Lumbar puncture was done in 122 of the 219 cases. Of this number there were 2 fatalities directly attributable to the lumbar puncture. The pressure was recorded in 112 cases. Of these, the pressure was elevated above 180 mm. of water in 90 (80 per cent). Of 79 cases in which the cerebrospinal fluid protein was determined, it was elevated above 45 mg. per cent in 60 (76 per cent). The cell count was determined in 96 cases. More than 5 white cells per c. mm. were present in 23; 30 showed the presence of red cells, while 52 had normal cell counts. Out of 66 cases in which pressure, protein, and cell count were all recorded, only 4 showed normal values for all 3 determinations.

Based on this experience, the cerebrospinal fluid in a case of glioblastoma multiforme is very likely to be abnormal in some respect. The information obtained, however, is nonspecific and is gained at the risk of a mortality rate of almost 2 per cent for the procedure of lumbar puncture.

Many of these lumbar punctures were performed by other services before the patient was referred to us, and a good many were done during the early years. Our present attitude is that lumbar puncture should be reserved for those cases in which the diagnosis is in considerable doubt and when it appears that valuable information of benefit to the patient can be thus obtained.

Roentgenograms of the skull are taken routinely. The results of this

examination are recorded in 191 of our cases. Abnormalities were present in 59 per cent; 32 per cent showed a pineal shift, 26 per cent had changes secondary to increased intracranial pressure, 2 per cent showed abnormal calcification, while 9 per cent had various other abnormalities. In addition to being "positive" in a respectably high percentage of cases, the roentgenograms of the skull may give information of specific diagnostic value. The presence of a mass lesion and its lateralization are often disclosed.

TABLE 2

Results of air studies

	Pneumoencephalogram	Ventriculogram
Number done	19	135
Result unknown	3	4
Result known	16—100%	131—100%
Localizing	3—18.7%	101—77.1%
Nonlocalizing	13—81.3%	30—22.9%
Indeterminate	2—12.5%	2— 1.5%
Abnormal, nonlocalizing	3—18.8%	2— 1.5%
Lateralizing only	0— 0%	6— 4.6%
False localization	0— 0%	5— 3.8%
Inadequate filling	8—50.0%	15—11.5%
Total abnormal	6—37.5%	114—87.0%
Fatalities	1— 5.3%	0

Electroencephalography was done in 90 cases. Of these 93 per cent were abnormal in some respect and only 7 per cent normal. Abnormality without localization occurred in 10 per cent; 49 per cent localized the lesion correctly while an additional 24 per cent gave a localization in the wrong lobe of the brain, yet close enough to be of some value; 9 per cent lateralized the lesion correctly without localizing it. In 1 case there was a localization in the wrong hemisphere. The figures speak for themselves. The electroencephalogram is without question a valuable diagnostic tool.

Air Studies. Short of surgery, the ultimate means of confirming the diagnosis of tumor and localizing the lesion has been an air study. The results of pneumoencephalography and ventriculography are compared in Table 2. Because the risk of a simple lumbar puncture is compounded in the pneumoencephalogram it is our present policy not to do this procedure knowingly in cases of tumor. Only a small number were done in this series. One out of 19 resulted in a fatality. Because of the small numbers involved the figures admittedly do not bear much weight. The results in this series, at any rate, were quite poor.

The yield of useful information from ventriculography is quite high, with accurate localization in 77 per cent. This appears particularly noteworthy since the series includes our early experiences with the procedure. In most

instances ventriculography was followed by craniotomy the same day. Any fatalities that might have followed were therefore scored against the craniotomy. The fact that no localization was obtained in 23 per cent of the cases emphasizes the importance of having an accurate history and neurological examination before becoming committed to surgery.

Arteriography was performed in only 21 cases, this series antedating the present vogue for this procedure. Of these 11 were abnormal; 10 (48 per cent) localized the lesion while 11 did not. Of those that failed to localize, 1 was lateralizing only, 2 were indeterminate, and 8 were inadequately filled. All were carotid injections. Bilateral studies were done in only 1 case, which was indeterminate. There were no fatalities. With the development of new techniques such as the use of the seriograph the future of arteriography is no doubt brighter than these results would indicate.

TREATMENT

Surgery. Surgical treatment was employed in 183 of 219 cases. Patients with craniotomy and tumor removal limited to biopsy are considered as surgically treated, as the procedure probably had some influence on the sub-

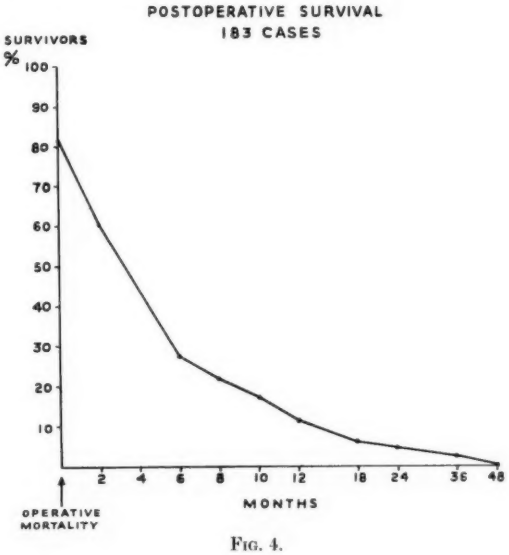

FIG. 4.

sequent course. A patient with needle biopsy via a burr hole, however, is considered untreated. Of the 36 untreated patients, 4 were dead on arrival at the hospital, 15 were undiagnosed prior to death, 10 were diagnosed but died before treatment could be instituted, while 7 were judged inoperable.

The postoperative survival of the 183 surgical cases is presented in Fig. 4. The operative mortality was 18.5 per cent, operative deaths being arbitrarily defined as any that occurred within 1 week of operation. About

50 per cent of the patients were dead within 3 months, almost 75 per cent within 6 months; 13 per cent survived over a year postoperatively. The longest survival was 48 months. In those cases in which more than one operation was performed the survival is computed from the date of the first procedure.

A single operation was done on 155 patients, 26 had two, 1 had three, while 1 had five procedures. Only actual attacks on the tumor are included in these figures. Procedures such as re-elevation of a bone flap for postoperative clot are not included.

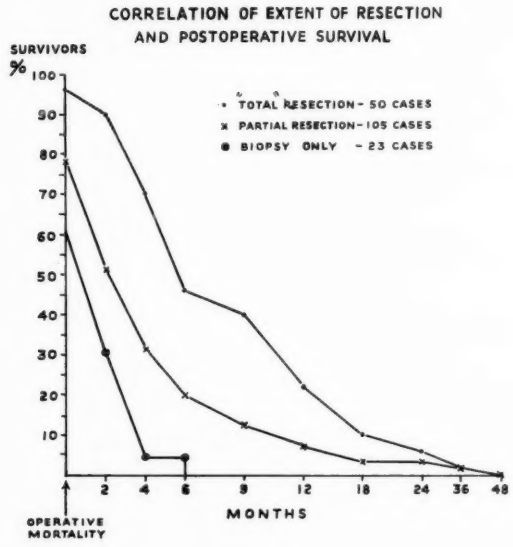

FIG 5.

The technique of the surgical attack upon brain tumors varies considerably, being governed by the various factors that determine operability—such as anatomical site and size of the tumor, the general condition of the patient, the neurological deficit—and also by the philosophy of the surgeon. We felt that it would be of interest to compare the results of various techniques. Based on the details reported in the surgeon's operative note, it has been possible to divide the cases into groups according to the extent of tumor resection, the type of external decompression, and the type of internal decompression.

With respect to the extent of tumor resection, it was possible to classify 178 of the cases; 50 patients had a grossly "total" removal of tumor in the estimation of the surgeon, 105 had a partial removal, while in 23 cases the tumor removal was limited to a biopsy. The survival curves of these 3 groups are presented in Fig. 5. The striking difference in operative mortality and

extended survival is quite apparent. It is clear that complete removal of all visible tumor tissue, if it can be accomplished, will give the patient the best chance of survival. However, it is obvious that the opportunity for carrying out such a "total" resection is limited by the various factors previously noted.

The type of decompression was noted in 176 cases; 51 patients had none, 95 had a small decompression, usually subtemporal, and 30 had a large decompression with removal of the bone flap. The first two groups had operative mortality rates of 17.6 per cent and 14.7 per cent respectively, with little

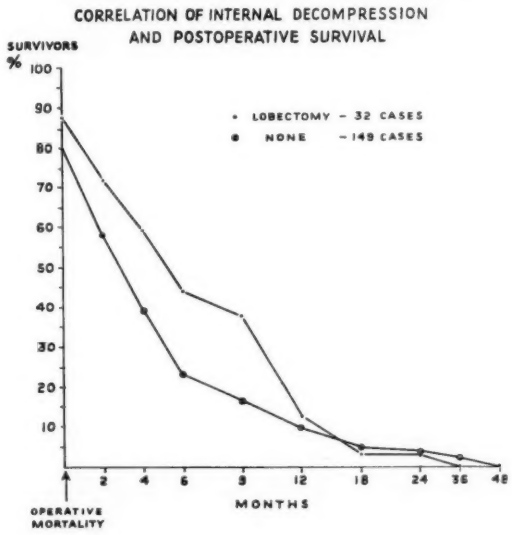

FIG. 6.

difference in the survival rates. The group with large external decompressions did not fare so well, having an operative mortality of 30 per cent and all the patients dead within 1 year. Removal of the bone flap in this clinic is reserved usually for patients with brain swelling or an inoperable tumor. The procedure undoubtedly enables many patients to survive a crisis and may prolong life a few months. The figures merely reflect the poor prognosis of the group of patients selected for removal of the bone flap.

Some degree of internal decompression accompanies any tumor removal, but occasionally a massive internal decompression is achieved by means of partial lobectomy. Out of 181 patients classified, 26 had a lobectomy incidental to removal of the tumor. Another 6 had a lobectomy in addition to the tumor removal, making a total of 32 lobectomies. The remaining 149 patients did not have a lobectomy. Comparison of the survival curves of the 2 groups (Fig. 6) indicates that the patients with lobectomy enjoyed a considerable advantage for the first 9 months. From 12 months on the 2

groups were quite similar. Our comments regarding "total" removal of visible tumor apply equally well here.

The evidence presented indicates that the most radical surgical procedure consistent with maintaining neurological function will accomplish the most for the patient in terms of survival. The more radical procedures also have a lower operative mortality.

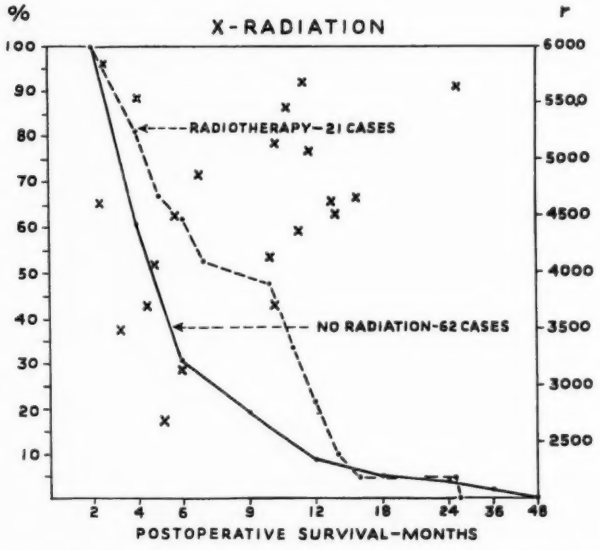

FIG. 7. Comparison of postoperative survival of 21 patients who completed radiotherapy within 60 days after operation with that of 62 patients who had surgery alone and were alive 60 days after operation. x indicates survival of each radiotherapy case plotted against tumor dose in r.

RADIOTHERAPY

Radiotherapy was used in 47 patients of whom 41 completed the prescribed course; 39 of these had surgical resection of the tumor, 1 had only a biopsy, and 1 had no surgery at all. Treatment was given at various times in the course of the disease, some patients being treated late in their course because of a symptomatic recurrence. It was possible to select a group of 21 patients all of whom completed their radiotherapy within 60 days after operation. The dose of radiation in these cases varied between 2700 and 5900 r tumor dose. In Fig. 7 the postoperative survival of these patients is compared with a group of 62 patients who had surgery alone and who were alive 60 days after operation. It is apparent that during the first 12 months there is a significantly greater percentage of survivors in the radiated groups. After the first year, however, the difference disappears. The radiation dose of each of the treated patients is plotted against the survival time.

Among the patients surviving less than 9 months there is a wide range of dosage. With a single exception, those surviving 9 months or more received over 4000 r tumor dose. The results of routine postoperative radiation in this small series indicate that a worth-while prolongation of the palliative effects of surgery may be obtained. We propose to use radiotherapy more generally in the future than was the case in this series.

THE EFFECT OF TREATMENT ON TOTAL DURATION OF ILLNESS

Sufficient information was available on 178 patients receiving the various types of treatment discussed above and on 30 patients receiving no treatment at all to allow us to compare these two groups.

Comparison of the duration of illness between the treated and untreated groups (Fig. 8) reveals a considerable difference in the number of survivors during the first year. We have seen that two-thirds of the postoperative

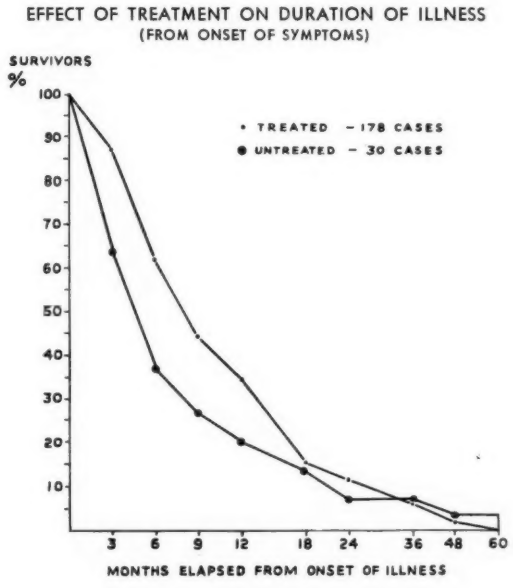

FIG. 8.

survivals are less than 6 months, the average being closer to 3 months. This extra 3 to 6 months seems to correspond to the early difference between the treated and untreated groups. It is of considerable interest that after the first year the percentage of survivors in the two groups is roughly the same. It would appear that the occasional long postoperative survival is because of the fact that the tumor happens to be a slow-growing one. An equal percentage of patients with untreated tumors last just as long.

POST-TREATMENT COURSE

Since all the presently known forms of treatment for glioblastoma are merely palliative, we cannot be satisfied with mere prolongation of life, laudable though it may be. It is pertinent to inquire also into the disability remaining after treatment. Of 172 treated patients whose disability status is known, 27.3 per cent died within 2 weeks of treatment, 33.1 per cent were left with severe disability, including such conditions as unconsciousness, hemiplegia, etc.; 27.3 per cent had slight disability, not requiring constant nursing care. Only 12.2 per cent were able to resume a useful occupation. We might say that 40 per cent had reasonably good results: slight or no disability.

RECURRENCE OF SYMPTOMS

If a patient is to benefit from treatment, how long can we expect this benefit to last? A recurrence is defined for our purposes as the development of symptoms indicative of progressive disease. We were able to document the question of recurrence in 143 of the 184 patients treated. There was no remission in 60 per cent. The deaths following treatment are included in this number. Only 27 per cent of the patients went 3 months without a recurrence; 15 per cent passed the 6 months' mark, while only 5 per cent went a year. The longest interval recorded was 29 months.

STATUS AT DEATH

As mentioned above, all of the 219 patients in this series are dead. In the cases in which the patient survived treatment, 130 deaths were from the tumor; 47 patients died during treatment or within 2 weeks; 35 died untreated. Death occurred in 3 cases from unrelated causes with tumor present; 4 patients died with the status of the tumor unknown. None of the patients died of an unrelated cause with no evidence of recurrence: there were no cures.

PATHOLOGY

In tabulating the various morphological characteristics of these tumors we have taken as our example in each case the first specimen obtained, usually a surgical specimen, but in some cases the autopsy specimen. This method offers the advantage of a uniform approach to each case, avoiding the dubious process of deciding which specimen is most representative in those cases in which serial specimens were available.

The primary site of the tumor is indicated in Table 3. There was a slight preponderance of tumors in the right hemisphere over the left. Growths arising primarily in midline structures were relatively rare.

The gross characteristics of 200 tumors are presented in Table 4. Most common were solid tumors, although cysts occurred frequently. Areas of necrosis were quite common (52 per cent), as were small scattered hemorrhages (40 per cent). Four of the tumors presented as solitary cysts with a

TABLE 3

Primary site of tumors
218 cases

Right hemisphere	109
Left hemisphere	91
Midline structures	18
Frontal lobe	50
Frontal-temporal	5
Frontal-parietal	8
Temporal lobe	47
Temporal-parietal	18
Parietal lobe	42
Parietal-occipital	9
Occipital lobe	8
Occipital-temporal	4
Occipital-temporal-parietal	5
*Diencephalon, corpus striatum	14
*Brain stem	5
*Corpus callosum	5

* Includes combined sites.

mural nodule, resembling astrocytomas. In only 6 cases was there grossly visible calcification (2 per cent of the roentgenograms of the skull in this series showed abnormal calcification).

The microscopic details of glioblastoma multiforme are well known. In establishing the diagnosis the criteria which we weighted most heavily were pleomorphism, proliferation of the intima of blood vessels, and the presence of mitotic figures. Unless at least two of these could be demonstrated the tumor was excluded from the series. The frequency of the various microscopic characteristics is given in Table 5.

The predominant type of cell was tabulated in 204 cases; 174 tumors presented a mixed picture with no single type of cell predominating. In 15

TABLE 4

Gross pathology of tumors
200 cases

Solid tumor	119
Cyst	77
Solitary cyst with mural nodule	4
Small hemorrhages	80
Massive hemorrhage	4
Necrosis	104
Calcification	6

TABLE 5

Microscopic pathology of tumors
206 cases

Pleomorphism	203
Multinucleated giant cells	174
Mitoses numerous	147
Mitoses rare	52
Proliferation of vascular intima	197
Overgrowth of vascular adventitia	67
Blood vessels numerous	190
Necrosis	193
Pseudopalisades	92
Hemorrhage	129
Calcification	14

tumors the predominant cell was the fibrillary astrocyte, in 7 it was the protoplasmic astrocyte, in 6 the spongioblast, and in 1 the astroblast.

It is commonly believed that the presence of mitotic figures indicates a more malignant or rapidly growing tumor. If this were true, one would suppose that the tumors with the most mitotic figures would be the most rapidly progressive. To test the validity of this assumption we compared the total duration of illness in a group of 142 patients with tumors having numerous mitotic figures with a group of 54 patients with tumors having rare or no mitotic figures. Interestingly enough, the survival curves for the two groups were almost identical.

SUMMARY

An unselected series of 219 cases of glioblastoma multiforme has been reviewed from the standpoint of natural history of the disease, diagnostic studies, treatment, and pathology.

Natural History. The sex incidence was 58 per cent males and 42 per cent females.

The age incidence was greatest in the fifth and sixth decades.

The total duration of the disease was under a year in 67 per cent of the cases; 11 per cent of the patients, however, lived 2 to 5 years. The duration was not related to the age or sex of the patient.

The duration of symptoms prior to diagnosis was less than 6 months in 70 per cent of the cases but 17 per cent of the patients had histories longer than a year.

The frequency of various symptoms is tabulated. Headache was most common. Seizures occurred in a third of the cases and were the initial symptom in half of these.

There was no evidence of familial incidence nor of a relationship with any other disease of the nervous system.

Diagnostic Studies. The cerebrospinal fluid is almost always abnormal in some respect. There was a mortality rate of 2 per cent for the procedure of lumbar puncture while the information gained was nonspecific. Routine use of this procedure is not recommended.

Roentgenograms of the skull were abnormal in 59 per cent of the cases.

Electroencephalograms were abnormal in 93 per cent and localized the lesion correctly in 49 per cent of the cases.

Pneumoencephalograms were done only 19 times with 1 fatality. The lesion was localized in only 3 cases.

Ventriculograms gave a correct localization in 77 per cent of 135 cases.

Arteriography was performed in only 21 cases with 48 per cent successful localization.

Treatment. There were 183 patients treated surgically, with an operative mortality of 18.5 per cent. Average postoperative survival was about 3 months. The more radical surgical procedures, including "total" removal of the tumor and lobectomy, offered the best prognosis with regard to operative mortality and survival time.

Of 47 patients receiving radiotherapy, 21 received a course of 2700–5900 r tumor dose completed within 60 days after operation. This group showed a significantly higher percentage of survivors during the first year when compared with a group who had surgery alone.

The effect of all present forms of treatment is to prolong life by 3 to 6 months. Long-term survivals are just as common among untreated patients as those treated.

Postoperative disability tended to be great. Only 40 per cent of the patients had slight or no disability.

There was no remission of symptoms in 60 per cent of the cases. Only 15 per cent of the patients went 6 months without a recurrence. There were no cures.

Pathology. The anatomical site, and gross and microscopic characteristics of these tumors are tabulated.

The number of mitotic figures seen is shown to bear no relationship to prognosis.

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HYPOPHYSECTOMY IN SEVERE DIABETES

I. NEUROSURGICAL ASPECTS*

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(Received for publication August 1, 1957)

OUR observations in the treatment of 15 patients with severe diabetic complications of the Kimmelstiel-Wilson type have been most interesting. All of these patients had severe loss of vision and varying degrees of nephropathy. Neurosurgical procedures consisted in 10 patients of complete surgical hypophysectomy and in the remaining 5, section of the pituitary stalk. During the past few decades tremendous progress has been made in the management of diabetic patients. The average duration of life, in all age groups, has increased from 13 years in pre-insulin days to about 49 years at the present time (Joslin) and with the advent of antibiotics the prognosis of these patients has further improved. However, this increase in life expectancy has been overshadowed by increasing incidence of severe diabetic retinopathy and nephropathy in juvenile diabetics, conditions that do not respond to careful diet or insulin. Today a juvenile diabetic may be expected to live 20 years or more only to be confronted with increasing blindness and other symptoms and signs of Kimmelstiel-Wilson's disease.

Following the classical experimental work of Houssay,[4] in which he showed that absence of anterior pituitary function modified pancreatic diabetes and rendered the animal highly sensitive to insulin and susceptible to severe hypoglycemia on fasting, there have been sporadic attempts to utilize the Houssay phenomenon in man. To achieve the same result Cushing[2] relieved a patient with severe diabetes by roentgen-ray therapy of the pituitary gland. The first surgical removal of the hypophysis for this purpose was performed by Puech on the service of Clovis Vincent on October 29, 1934, and reported by Chabanier *et al.*[1] No other reports of hypophysectomy for diabetes were found in the literature until those of Luft and Olivecrona[7] in 1953, who described their experience in 4 cases and subsequently reported the largest series to date—20 cases.[8] Other reports of hypophysectomy are those of Kinsell *et al.*[5,6] and Schimek.[11]

MATERIAL AND METHODS

The 15 patients who are the subject of this report varied in ages from 19 to 61 years. Four of them were females and 11 were males. They had been known diabetics for periods ranging from 9 to 29 years. One of these pa-

* Presented at the meeting of the Harvey Cushing Society, Detroit, Michigan, April 27, 1957.

tients was a pituitary dwarf and one other was acromegalic. These patients all had marked diabetic retinopathy with loss of vision and some degree of nephropathy (Kimmelstiel-Wilson). Hypophysectomy was performed in 10 patients from November 1954 to June 1956, and the pituitary stalk was sectioned in 5 patients from September 1956 to January 1957 (Tables 1 and 2).

TABLE 1

Hypophysectomized diabetics

Patient Date of Op.	Age Sex	Years Diabetic	Preop. Insulin	Postop. Insulin	Preop. B.P.	Postop. B.P.	Retinopathy Vision	Renal Function	Daily Maintenance	Result
A.P.J. 11- 8-54	34 M	14	75 L E N T E	12 L E N T E	168/90	140/90	4+ Blind	Albumin but good renal function	Cortisone 50 mg. Thyroxine 300 μg.	Improved with return of useful vision, then death in hypoglycemia 26 mo. postop.
J.A.S. 1- 9-56	23 F	17	60 L E N T E	23 L E N T E	130/90	128/90	4+ Blind OD. Good OS	Albumin but good renal function	Cortisone 25 mg. Thyroxine 200 μg.	Improved vision, OS excellent. Feeling well. Back at work
A.A.K. 3- 8-56	42 M	29	50 N P H	30 L E N T E	200/100	136/100	4+ Barely useful vision	Albumin. Poor renal function	Cortisone 50 mg. Thyroxine 100 μg.	Mildly improved, then death in hypoglycemia 3 mo. postop.
D.B.Z. 3-26-56	27 F	21	35 L E N T E	15 L E N T E	120/70	120/70	4+ Nearly blind	Albumin but good renal function	Cortisone 37.5 mg. Thyroxine 200 μg.	Vision markedly improved, then death in hypoglycemia 3 mo. postop.
E.A.S. 4-20-56	28 M	21	65 N P H	35 L E N T E	140/100	128/80	4+ Blind OS. Good OD	Albumin but good renal function	Cortisone 25 mg. Thyroxine 200 μg. Testosterone 25 mg.	Greatly improved in all respects. Feeling well. Back at work
O.O.S. 5- 8-56	61 M	27	60 N P H	20 L E N T E	150/90	140/90	4+ Totally blind	Albumin free and good renal function	Cortisone 25 mg. Thyroxine 200 μg.	Feels well but remains totally blind
F.W.J. 5-18-56 Dwarf	21 M	17	45 N P H		160/100		4+ Almost blind	Heavy albumin and poor renal function		Died 36 hrs. postop. from severe diabetic nephropathy and postop. cerebral edema
M.S. 5-26-56	19 F	9	90 N P H	30 L E N T E	140/100	132/72	4+ Almost blind	Albumin but good renal function	Cortisone 25 mg. Thyroxine 200 μg.	Greatly improved in all respects. Feeling well
F.W.K. 6- 7-56 Acromegalic	50 M	15	50 P Z I	25 L E N T E	150/100	128/88	4+ Almost blind	Clear and good renal function	Cortisone 37.5 mg. Thyroxine 200 μg.	Greatly improved in all respects. Resumed former activities
C.C.W. 6-21-56	28 M	23	55 N P H	30 L E N T E	200/120	150/104	4+ Almost blind	Albumin but good renal function	Cortisone 37.5 mg. Thyroxine 200 μg.	Improved but remained totally blind. Died 7 mo. postop. from hypoglycemic shock

TABLE 2

Section of pituitary stalk in diabetics

Patient Date of Op.	Age Sex	Years Diabetic	Preop. Insulin	Postop. Insulin	Preop. B.P.	Postop. B.P.	Retinopathy Vision	Renal Function	Daily Maintenance	Result
J.A.G. 9-13-56	51 M	26	30 N P H	10 L E N T E	175/120	160/100	3+ Vision preserved	Albumin. Impaired renal function	Cortisone 25 mg. Thyroxine 200 μg.	Improved, then death in hypoglycemia 2 mo. postop.
E.A.M. 12-3-56	49 F	26	60 N P H	40 L E N T E	196/92	120/90	4+ Blind OS. Poor OD	Albumin but good renal function	Cortisone 25 mg. Thyroxine 100 μg.	Diabetes improved. Vision?
J.H.W. 1-9-57	55 M	14	32 N P H	None	144/82	116/60	4+ Blind OS. Fair OD	Albumin. Fair renal function	Cortisone 12.5 mg. Thyroxine 100 μg.	Diabetes improved. Vision?
H.W.B. 1-21-57	28 M	20	65 N P H		180/106 130/90		4+ Blind OS. Almost blind OD	Albumin. Impaired renal function		Died 4th day postop.
C.J.E. 1-19-57	43 M	17	40 N P H		170/100		4+ Blind OS. Almost blind OD	Albumin. Fair renal function		Died 8th day postop.

A subfrontal approach, using a "2-inch" craniotomy on the side of the blind eye, was employed in all cases. The cerebrospinal fluid was drained before opening the dura mater by a T-shaped incision, the horizontal limb of the T being placed at the center of the "2-inch" trephine opening with the vertical limb at the direction of the roof of the orbit. This was found satisfactory to protect the brain, which is very important in these diabetic patients. An incidental observation during craniotomy was the unusual yellowish color of the bone. The rest of the surgical technic in cases of hypophysectomy was essentially the same as described by Olivecrona[7] and subsequently by Ray.[9] Section of the pituitary stalk was performed after a similar exposure. The stalk was divided between two tantalum clips immediately above the diaphragma sellae and a piece of polyethylene film was placed over the distal end. Endotracheal anesthesia was used in all of our cases. Arfonad was employed in 6 of our hypophysectomies and in none of our sections of the pituitary stalk. Blood transfusions were given to 7 of the hypophysectomy patients during or after surgery, but in none of the cases of section of the stalk was this necessary. All of these patients received cortisone pre- and postoperatively with dosages ranging from 200 to 300 mg. daily.

RESULTS

In Tables 1 and 2 results are shown for each patient with regard to insulin requirement, changes in blood pressure, and retinal and renal changes. There was a consistent and marked decrease in insulin requirement postoperatively which is also illustrated in Fig. 1. Average blood pressure read-

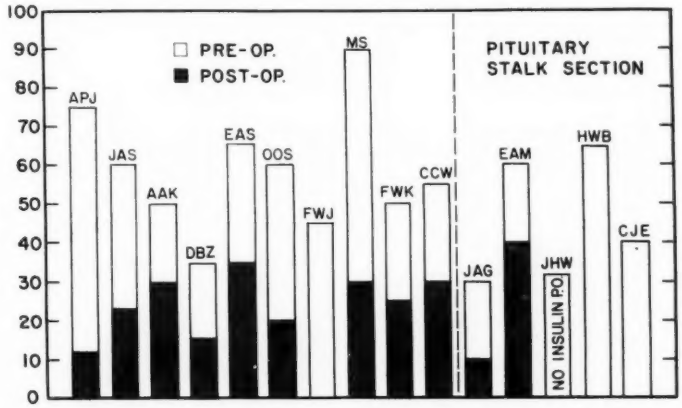

FIG. 1. Pre- and postoperative insulin requirements of hypophysectomized diabetic patients.

ings postoperatively were all lower than preoperatively except in 1 case (see also Fig. 2). There was consistent improvement in the diabetic retinopathy and return of vision in some of the cases. For example, patient M.S. was blind to the extent that she was unable to move about the room without assistance. At the present time, 14 months postoperatively, she is able to read print of

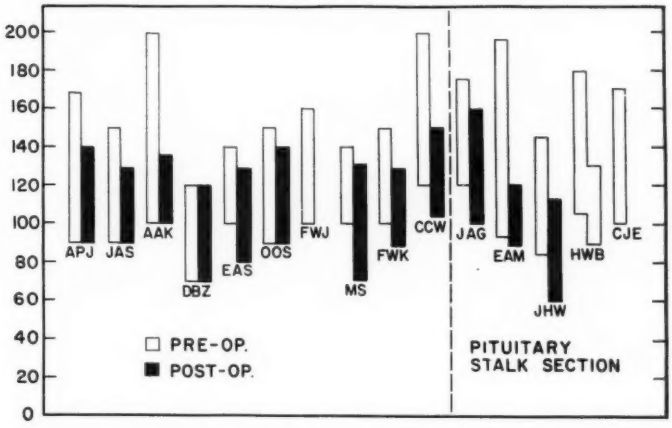

FIG. 2. Pre- and postoperative blood pressure of hypophysectomized diabetic patients.

ordinary size in the newspaper. Patient F.W.K. has also had a comparable return of vision after the loss preoperatively of almost all useful vision. We believe these results may be attributed to reabsorption of old hemorrhage without the occurrence of additional bleeding. One patient, C.C.W. (Table 1), who was almost blind preoperatively, suffered a total loss of vision postoperatively. There was some improvement in diabetic nephropathy. After discharge from the hospital these patients were maintained on cortisone between 25 and 50 mg. and thyroxine from 100 to 300 μg. daily. Three patients died after surgery—2, 4, and 8 days. Five patients died after discharge from the hospital from 3 to 26 months after hypophysectomy. Severe, prolonged hypoglycemia was the cause of death in all cases with the exception of the following instances:

(1) F.W.J. died from severe diabetic nephropathy and cerebral edema.

(2) H.W.B., who died 4 days postoperatively, had a sudden unexplained elevation of blood pressure to over 300 systolic as the frontal lobe was being retracted. There was no apparent bulging of the brain or bleeding. Pituitary stalk was sectioned about an hour later, and it was necessary to use mild electrocoagulation of the proximal end. This is the only case in our series in which any coagulation of the proximal end of the stalk has been done. Marked elevation of systolic blood pressure above 300 persisted for several hours and then decreased. At this time the patient began to respond and with the exception of marked diabetes insipidus his condition appeared to be satisfactory until he died very suddenly on the 4th postoperative day. Postmortem examination showed severe coronary sclerosis and pulmonary edema and hypertensive encephalopathy in addition to severe diabetic nephropathy, hypoplasia of the pancreas, and extensive necrosis of the pituitary (Figs. 3 and 4).

(3) In C.J.E. an unexplained intracerebral hemorrhage developed as soon as the optic nerve was exposed. There was a sudden rise in blood pressure, with marked herniation of the frontal cortex through the trephine. Twenty-five cc. of intracerebral blood were aspirated, but it was necessary to resect

FIG. 3. *H.W.B.* Frontal section of hypophysis (patient died 4 days after division of pituitary stalk) The light area indicates necrosis of the major portion of the gland. Note the marked arteriosclerotic change in the blood vessel of this 28-year-old patient (internal carotid artery).

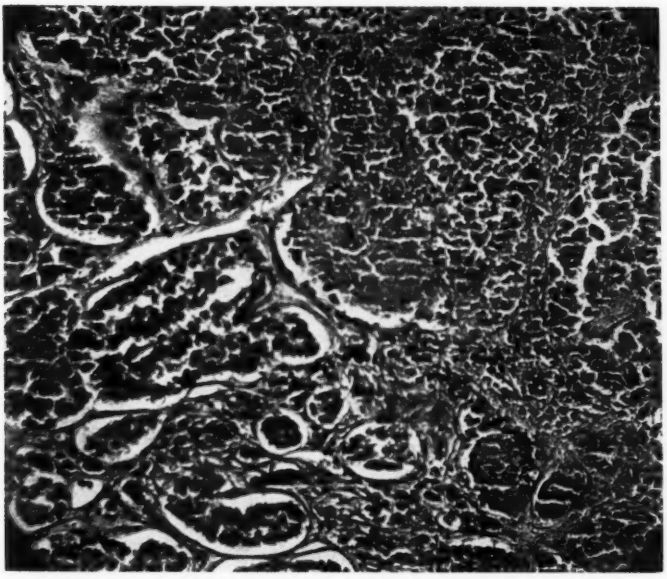

FIG. 4. Higher magnification of Fig. 3 at the junction of necrotic and normal glandular tissue.

the tip of the frontal lobe. This was the only patient in our series on whom a partial frontal lobectomy was done. The pituitary stalk was sectioned and, after a very stormy course, the patient died 8 days postoperatively. The findings at autopsy indicated that bronchopneumonia (*Staphylococcus aureus*) and purulent tracheobronchitis were the chief causes of death. In addition, moderate diabetic nephropathy, coronary atherosclerosis, subarachnoid hemorrhage, and focal necrosis of the pituitary were found (Fig. 5).

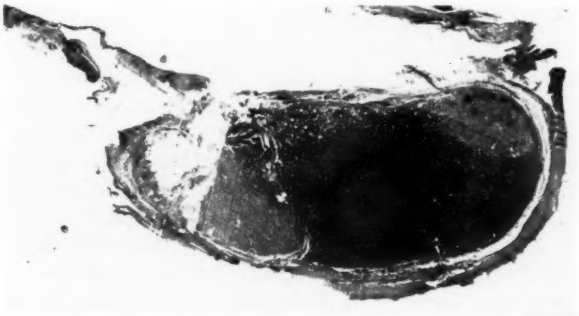

FIG. 5. *C.J.E.* Sagittal section of hypophysis (patient died 8 days after division of pituitary stalk). There is a very small area of necrosis in the anterosuperior pole of the anterior lobe in marked contrast to the extent of degeneration seen in Fig. 3.

On the basis of this limited experience section of the hypophysial stalk does not appear to be the physiological equivalent of total hypophysectomy, both from the standpoint of practical therapeutic results and physiological studies. Autopsy findings are believed to provide an explanation for this observation in the form of a wide variation in extent of pituitary necrosis resulting from the former surgical procedure.

DISCUSSION

Our results confirm the observations of Luft *et al.*[8] with regard to the decrease of insulin requirement, changes in blood pressure, and retinal and renal improvement, even though half of our patients were much older.

Extensive metabolic and endocrine studies on these patients have been carried out. These involve evaluation of various thyroid, adrenal, pituitary, hypothalamic and renal functions and will serve as the basis for a separate report.[3]

To our knowledge section of the pituitary stalk has not been reported previously for severe diabetes. Russell[10] suggested that division of the stalk at its junction with the gland would have the same effect as hypophysectomy in the treatment of advanced carcinoma of the breast. Our experience casts some doubt on this belief and suggests that there is a great variation in the amount of the destruction of anterior lobe as a result of section of the pituitary stalk. This is illustrated by microscopic studies in 2 cases which came to autopsy. In 1 patient necrosis of anterior pituitary is very extensive whereas in another patient there is only a small area of necrosis (Figs. 3, 4 and 5). This is perhaps because of variation in the vascular supply, namely anastomoses between the superior and inferior hypophysial arteries. This variability may account for the observation that section of the pituitary stalk is not parallel to hypophysectomy functionally as far as improvement in vision and alteration in endocrine assays are concerned.

CONCLUSION AND SUMMARY

Results of surgical treatment of 15 patients with severe diabetes have been analyzed. Hypophysectomy was performed on 10 of these patients and section of the pituitary stalk on another 5. Our evidence suggests that these two procedures are not equivalent. At present it is our opinion that hypophysectomy is not indicated as a routine therapeutic method in patients with advanced juvenile diabetes. However, further studies and re-evaluation are indicated. Major renal insufficiency is a contraindication for surgery, and the procedure should not be done in patients who will not follow instructions regarding insulin and diet postoperatively. Teamwork between neurosurgeon and endocrinologist as well as careful follow-up are essential. Hypophysectomy causes definite improvement in retinopathy and some improvement in nephropathy. It transforms a severe diabetic to a mild one as far as insulin requirement in concerned, but does not reverse permanent vascular changes that have already occurred. Results in some of our surviv-

ing patients have been sufficiently impressive that we feel hypophysectomy may have a place in the management of selected patients with severe diabetes and Kimmelstiel-Wilson's disease. There is reason to hope that with improved selection of cases and experience in postoperative management and cooperation of patients the long-time useful survival of the victims of this dreadful disease will be increased.

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PYOGENIC NEUROSURGICAL INFECTIONS IN KOREAN BATTLE CASUALTIES

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(Received for publication August 19, 1957)

IT IS generally accepted that the incidence of antibiotic-resistant bacteria in closed communities is more or less related to widespread use of the drug over an extended period of time. That antibiotic-resistant infections in war wounds likewise should attend routine use of penicillin for prophylaxis of infection would seem logical. Documentary evidence supporting this hypothesis has been obtained in World War II and in Korea. Roy *et al.*[5] made a study of contamination and infection of soft-tissue wounds in 1944–45. They noted an incidence of 17 per cent penicillin-resistant strains of staphylococci in 94 control cases, and an incidence of 49 per cent among 69 penicillin-treated patients. Lindberg and Parrott,[2] in a bacteriological study of 25 casualties in Korea, found that two-thirds of the micrococci isolated from their wounds were resistant to penicillin. This communication reports clinical and bacteriological studies in neurosurgical Korean battle casualties.

GENERAL PROCEDURE

This report is based on 58 consecutive patients treated at the Neurosurgical Center, Tokyo Army Hospital, between February 1951 and May 1952. The majority of these had been wounded in action in Korea, and had received initial surgery by one of the neurosurgical teams or on hospital ships in the Korean Theater, prior to evacuation to Japan. Practically all had received daily intramuscular injections of penicillin and streptomycin from the time of injury to admission. These patients had pyogenic infections of the central nervous system, or in craniectomy or laminectomy wounds.

Shortly after admission swabs, needle-puncture aspirates, or tapped spinal fluids were taken from infected areas in every instance. The primary objective was to obtain laboratory guidance in selection of appropriate antimicrobial therapy. In Korea only penicillin and streptomycin were freely available. In our hospital, chloramphenicol (Chloromycetin), also limited stocks of chlortetracycline (Aureomycin) and oxytetracycline (Terramycin), were at hand. For the purpose of obtaining rapid data on sensitivities to antibiotics, the medicated disc-blood agar plate method was established at Tokyo Army Hospital in January 1951 by one of us (E.J.P.).*

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† Letterman Army Hospital, San Francisco, California.

* Commercially prepared discs containing the following concentration of antibiotics: penicillin 1 and and 2 units; and streptomycin, chloramphenicol, chlortetracycline and oxytetracycline, each 10 micrograms.

The bacteriological studies were performed by Major Claude Lenn (MSC) and assistants. Within an hour of receipt of material for culture, pus, exudate, or spinal fluid was streaked on blood agar plates, medicated discs containing a measured amount of each antibiotic were spaced over the surface of the plates, and the plates were incubated. At the same time additional material was inoculated in fluid media, thioglycolate broth or cooked meat media. By this technic it was frequently possible to obtain a report within 24 hours as to the predominating aerobic species of microorganisms present as well as their *in vitro* sensitivities to the antibiotics tested. It was possible, therefore, to select the antibiotic or antibiotics showing *in vitro* sensitivities for a pure or mixed infection. Bacterial growths were categorized on the basis of colony form, presence or absence of a zone of hemolysis, as well as morphology and gram-stain reaction. Anaerobic and special culture studies and detailed classification of the organisms were resorted to primarily in the instances of persistent or unresponsive infections.

RESULTS

Location of Infection. The areas from which a positive culture was obtained are listed in Table 1. It will be noted that about one-half (30) of the 58 patients had positive bacterial growths in a single location, and the other half (28) had positive cultures from several different locations. Seven patients had infections limited to the scalp only. These are included because infection of the scalp was shown ultimately to be the locus of origin for some of our most severe cases of meningitis. Confirmation of infection by bacteriological studies was possible in the majority of cases. In a few instances "sterile" (no growth) brain abscess cavities were encountered at surgery, and

TABLE 1

Location of infection

	No. of Patients	Total
Scalp only	7	20
Scalp and other areas	13	
Subgaleal only	11	32
Subgaleal and other areas	21	
Spinal fluid only	6	22
Spinal fluid and other areas	16	
Brain only	2	16
Brain and other areas	14	
Ventricle only	0	8
Ventricle and other areas	8	
Paraspinal only	4	4

in other cases of patients with brain fungus or with signs of meningitis, the cultures of spinal fluid were negative. Suppression of growth caused by concurrent systemic antibiotic therapy and/or the failure to culture microorganisms with fastidious requirements of growth were implicated in these situations.

Bacteriologic Data (Table 2). Gram-positive micrococci, the majority of which were hemolytic staphylococci and the others, beta hemolytic or nonhemolytic streptococci were the most frequently isolated microorganisms. Sporulating gram-positive rods (*B. subtilis* 3, *Clostridium welchii* 3, *unidentified* 2) were the least common isolates. The combination of gram-positive cocci and gram-negative bacilli (coliforms, Proteus species, Pseudomonas species) was the second most frequent bacteriological finding.

Antibiotic sensitivity studies revealed that the bacterial isolates were susceptible to penicillin in only 10, and to streptomycin in only 9 of the 58 cases. This was not surprising since practically all the patients had been receiving these antibiotics since injury in Korea, and their infections were static or progressive in the face of this therapy. The tetracyclines (Aureomycin and Terramycin) were of potential value in 32 of the 58 cases. The early finding of the superiority of chloramphenicol against penicillin- and streptomycin-resistant microorganisms was sustained throughout the study; the drug was bacteriologically the one of choice for therapy in 47 of the 58 cases. Clinically, chloramphenicol had the additional merit of rapidly build-

TABLE 2

Bacteriological data and results of therapy

Bacteriology	Number Antibiotic-Sensitive*					Total Number of Patients	Clinical Result	
	P	S	A	T	C		Recovered	Died
Gram-positive cocci	10/32	8/32	16/32	15/32	23/32	32	28	4
Two different strains of gram-positive cocci	0/1	0/1	0/1	0/1	1/1	1	1	0
Gram-positive rods, gram-positive cocci	0/2	0/2	1/2	2/2	2/2	2	2	0
Gram-positive cocci, gram-negative bacilli	0/13	0/13	4/13	9/13	12/13	13	11	2
Gram-positive bacilli	0/2	0/2	1/2	2/2	2/2	2	2	0
Gram-positive rods, gram-negative bacilli	0/1	1/1	0/1	0/1	1/1	1	1	0
Gram-negative rods	0/4	0/4	0/4	2/4	4/4	4	4	0
Three or more various gram-positive and gram-negative organisms	0/3	0/3	0/3	2/3	2/3	3	1	2
Total	10/58	9/58	22/58	32/58	47/58	58	50	8

* P = Penicillin S = Streptomycin A = Aureomycin
T = Terramycin C = Chloromycetin
Numerator = Antibiotic-sensitive

ing up a high concentration in the cerebrospinal fluid[4] and proved to be the most universally effective available antibiotic. We saw no evidence of blood dyscrasias traceable to chloramphenicol medication, even in some patients who were on antibiotic medication and under observation at Tokyo Army Hospital for greater than a hundred days.

There were 7 patients with organisms resistant to all 5 antibiotics. The 6 who had meningitis or cerebritis died and the seventh, who had a scalp infection only, survived. There were 2 other patients who died, bringing the total to 8.

Factors Related to the Cause of Infection. All penetrating wounds are potentially infected. The keystone of prevention of infection in penetrating wounds of the brain is the earliest possible definitive surgery. The initial operation should be the final and complete one. The removal of all devitalized tissue and foreign bodies must be achieved. The factors implicated as the cause of infection in each of the 58 patients in this series are listed in Table 3. Retained bone fragments and inadequate debridement of the brain

TABLE 3

Factors implicated as cause of infectious complications

Retained bone fragment(s)—inadequate debridement	25
Retained large metallic foreign body (1×3 cm.)	1
Inadequate closure of scalp and dura mater	16
Delay of initial surgery, 48 hours or more	10
Dural leak through eye	1
Dural leak through ear	1
Bacterial endocarditis, metastatic brain abscess	1
Undetermined	3
Total	58

wound were the most common causes, and were implicated in 25 of the 58 infections. Sixteen patients had inadequate closure of the scalp and dura mater—the second most frequent cause of failure to prevent infection. In several instances a beautiful operation was spoiled by closing the edges of the skin under tension with resultant separation of the edges of the skin, infection of the dural graft, cerebritis and meningitis. It is important to excise the wound of entry, then to make up the scalp deficit, if necessary, by rotating a scalp flap over the site of the craniectomy and applying a split-thickness skin graft to the intact periosteum of the donor site.

In 10 instances the initial surgery was delayed beyond 48 hours. Five of the patients in this group had sustained facial or eye wounds without immediately evident brain damage. Diagnosis was made after the appearance of signs of meningeal irritation. Roentgenograms showed intracranial metallic foreign bodies but no bone fragments. Often the wound of entry into the base of the skull was not evident. In this group surgery was accomplished on an average of 12 days after injury and usually was preceded by ventriculog-

raphy. Because of the tactical combat situation, 2 patients were isolated from medical attention for more than 48 hours. Another 2 patients who had scalp lacerations first sought medical aid 7 and 16 days after injury and severe cellulitis of the scalp had developed. One patient had a penetrating wound of the abdomen with intra-abdominal hemorrhage. A laparotomy was done, then 3 days later a craniectomy, and meningitis developed. In 3 patients the basis for infectious complications was obscure.

Clinical Management and Results of Treatment. Practically all patients who had extradural infection required open treatment with resection of the dural graft and subsequent closure of the dura mater and scalp. The mode of treatment of cerebral fungus (cerebritis) employed in these patients had been outlined by Meirowsky and Harsh,[3] and by Courville *et al.*[1] The frequency of infections complicating transventricular wounds of the brain in this series of patients has been reported previously by one of us (G.T.W.).[6]

Ten patients (3 with meningitis and 7 with scalp and/or extradural infections) did not require additional surgery, as their infection responded to antibiotics and the previous surgery appeared adequate. Of these 58 patients, 48 required one or more additional operations at Tokyo Army Hospital in an attempt to bring the infection under control. Of these, 30 patients required 2 or more operations; usually these consisted of debridement followed by delayed closure. One patient, who survived, required 8 operations and 101 days of adjunct antibiotic therapy before infection was brought under control.

In general, antibiotics were given for a period of at least 10 days after all evidence of infection subsided. Some patients who had severe infections were continued on antibiotics for as long as 3 weeks after reports of sterile culture were obtained. Antibiotics were administered orally or systemically, and no intrathecal injections were used.

A summary of fatal cases is given in Table 4.

SUMMARY

1. Retained bone fragments, improper closure of scalp and dura mater, and delay of definitive surgery beyond 48 hours were the principal factors implicated in development of infection in neurosurgical penetrating wounds in 58 patients injured in Korea.

2. Whereas penicillin and streptomycin are probably useful adjuncts to precise definitive surgery in the prevention and treatment of penetrating wounds of the head and spinal cord, they are not effective unless initial surgery has been complete.

3. Uncontrolled infections in penetrating neurosurgical wounds are usually caused by gram-positive cocci, gram-negative bacilli, or combinations of both. Frequently the same organisms are isolated from more than one location.

4. Prophylactic systemic therapy with penicillin and streptomycin has been associated with a high incidence of drug-resistant micrococci in persisting infections.

TABLE 4

Analysis of deaths

Case	Delay in Surgery	Initial Surgery	Cause of Failure to Prevent Infection	Culture and antibiotic Sensitivity	Days Hospitalized	Cause of Death
1	12–24 hrs.	Hospital Ship Korea	Dural leak	Staphylococci sensitive to Aureomycin, chloramphenicol and Terramycin	4	Meningitis, pneumonia, respiratory obstruction
2	48 hrs.	Tokyo Army Hospital	Scalp infection with spread	Hemolytic *Staphylococcus aureus*, resistant to all five antibiotics	50	Fulminating cerebritis
3	48 hrs.	Hospital Ship Korea	Retained bone fragment	*E. coli, pseudomonas*, hemolytic staphylococci, sensitive to chloramphenicol and Terramycin	69	Fulminating cerebritis
4	44 days	Neurosurgical Team—Korea	Delay, wound of entry to brain via face	Nonhemolytic staphylococci, resistant to all five antibiotics	54	Meningitis, ventriculitis
5	4 days	Hospital Ship Korea	Wound to under surface of brain via orbit	Gram-negative rods and gram-positive cocci, resistant to all five antibiotics	102	Meningitis, hepatitis, transfusion reaction
6	12 hrs.	Mobile Army Surgical Hospital	Retained bone fragment	Hemolytic staphylococci and gram-negative rods resistant to all five antibiotics	38	Meningitis
7	12 days	Neurosurgical Team—Korea	Delay—retained bone fragment	Gram-negative rods and gram-positive cocci resistant to all five antibiotics	85	Cerebritis
8	12–24 hrs.	Marine Mobile Hospital Korea	Retained bone fragment	Hemolytic staphylococci, resistant to all five antibiotics	48	Cerebritis

5. Laboratory guidance for specific antimicrobial therapy is essential in these circumstances. The medicated disc-blood agar plate method of testing sensitivity to antibiotics provides useful information within 24 hours of submitting material for culture in most instances.

6. Chloramphenicol was best, the tetracycline antibiotics were intermediate, and penicillin and streptomycin were the least effective antibiotics on the basis of *in vitro* sensitivities. Chloramphenicol has the additional advantage of providing therapeutic concentration in cerebrospinal fluid following systemic administration.

7. Saturation of blood and tissues with an antibiotic effective for the infecting microorganisms gives protection against dissemination of infection during excision of loci of infection.

8. In a series of 58 cases of neurosurgical infections, 50 patients recovered

and 8 died. In 6 of the 8 fatal cases the infections had been resistant to all of the 5 available antibiotics.

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DESTRUCTION OF THE HYPOPHYSIS WITH RADIOACTIVE COLLOIDAL CHROMIC PHOSPHATE IN CANCER OF THE PROSTATE

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(Received for publication August 20, 1957)

TREATMENT of metastatic cancer of the prostate by hypophysectomy has been reported by several investigators.[8,10,14] This therapy has been tried in the hope that the tumor cells might be dependent to some degree upon the secretion of adrenal androgens, or upon growth hormone or some other secretion of the hypophysis. The number of cases of cancer of the prostate treated by destruction of the pituitary body is not yet great enough to evaluate adequately the effectiveness of this treatment. Luft and Olivecrona[8] were able to find in the literature 3 cases of cancer of the prostate in which remission occurred after hypophysectomy. They added 5 of their own, making a total of 8 remissions in 16 patients treated by surgical hypophysectomy. Precise interpretation of these data is difficult since orchiectomy had not been performed in all instances. For instance, the patient of Luft and Olivecrona,[8] who had the longest remission (over 24 months), had not had orchiectomy prior to hypophysectomy. It is entirely possible that the prolonged remission in this case may have been caused entirely by the cessation of testicular function. The patient reported by Scott[14] who had a good remission after hypophysectomy also had not had orchiectomy. On the other hand, the reported data are not complete enough to exclude the possibility that at least some of the patients who received no benefit from hypophysectomy might not have been completely hypophysectomized.

The technical difficulties of performing a complete hypophysectomy have limited the use of this operation.[1] In order to avoid surgical hypophysectomy, external irradiation of the pituitary body has been tried. Because of the location of the pituitary body and its resistance to irradiation, it had not been possible to achieve complete permanent interruption of pituitary function with this method.[7] However, the recent use of high-energy proton irradiation of the pituitary body may have solved this difficulty.[9] Internal irradiation of the gland has been tried with several radioisotopic techniques including the implantation of yttrium pellets,[16] radon seeds,[5] and gold.[1,6]

Recently, Rothenberg *et al.*[11] attempted the direct injection of radioactive colloidal chromic phosphate containing P-32 into the substance of the gland in 6 patients with neoplasms. Phosphorus-32 would seem to offer some advantages over the other radioisotopes used for this purpose, because of its

relatively long half-life, its energetic beta particle, and because it does not produce gamma radiation. To our knowledge, this preliminary report of Rothenberg *et al.* and one other preliminary report by the same group[12] are the only articles published describing the use of radioactive colloidal chromic phosphorus for destroying the pituitary gland. They performed this procedure in 3 cases of carcinoma of the breast, 2 cases of thyroid carcinoma and 1 case of prostatic carcinoma. For this purpose, they injected 2 ml. of colloidal chromic phosphate containing 10 mc. of P-32 directly into the pituitary substance. We have performed this procedure in 6 patients with far-advanced carcinoma of the prostate in order (1) to evaluate the effect of destruction of the pituitary body on cancer of the prostate, and (2) to investigate the clinical usefulness of this particular method of destroying the pituitary body. The results obtained are presented.

TECHNIC

After a frontotemporal flap is turned, the frontal lobe is retracted gently until the diaphragm sellae is identified. With the exception of the first patient, 0.5 to 1.5 ml. of a solution containing 9–10 mc. of P-32 (Table 2) as colloidal chromic phosphate was injected into the substance of the gland, using a 25-gauge needle. Three ml. of this solution were injected into the pituitary body of the first patient. The subsequent patients received less than 1.5 ml. of the chromic phosphate solution because injections of aqueous methylene blue into the normal pituitary body at autopsy showed that volumes greater than this resulted in marked overflow of the dye. At least four sites of injection were used in an attempt to distribute the radioactivity throughout the gland. Methylene blue was added to the colloidal material so that leakage of the radioactive solution superiorly could be detected and removed by washing with copious amounts of saline. The pituitary stalks in Cases 4, 5 and 6 were clipped and severed prior to the injection of P-32.

Preliminary studies performed on normal pituitary glands at autopsy had shown us that the injected material diffuses fairly evenly throughout the substance of the gland. Usually, any excess of injected material escapes from the sella by migrating laterally and inferiorly under and between layers of the dura mater. Dye can be identified beneath the dura mater behind the posterior clinoids when more than 1 ml. is injected. There is also leakage superiorly out through the top of the sella when large volumes are injected, but when the injected volume is less than 1 ml. this does not usually occur. Since the sella has a capacity of less than 1 ml. it would seem reasonable to limit the volume injected to less than this amount in order to minimize leakage and in this way avoid excessive irradiation of nearby neurologic structures.

CASE MATERIAL

The patients chosen for this procedure had far-advanced metastatic carcinoma of the prostate gland. Each had had symptomatic improvement following orchiectomy except Patient 2 who had not improved after this procedure and Patient 4 who had refused orchiectomy. All patients required narcotics for relief of pain. Each of these patients had become refractory to estrogen therapy before pituitary destruction was attempted. All patients had biopsy proof of prostatic carcinoma. Table 1 summarizes the clinical and

TABLE 1

Clinical summary of 6 patients with prostatic carcinoma treated by radiation of the hypophysis

Case No.	1	2	3	4	5	6
Age of patient	62	62	59	59	66	65
Previous therapy						
Months since transurethral resection	27	1	23	—	—	13
Months since orchiectomy	26	1	4	3	—	12
Response to orchiectomy	Yes	No	Yes	Yes	—	Yes
State on admission						
Pain	Yes	Yes	Yes	Yes	Yes	Yes
Bony metastasis	Yes	Yes	Yes	Yes	Yes	Yes
Laboratory data before surgery						
Hemoglobin gm.%	9.9	8.8	12.0	8.7	14.0	11.0
W.B.C.$\times 10^{-3}$	11.0	7.0	16.0	9.2	9.9	7.8
Alkaline phosphatase B.U.	4.0	66.0	7.8	17.0	6.6	24.0
Acid phosphatase B.U.	4.8	0.5	1.0	4.8	2.7	0.7
N.P.N. mg.%	45.0	18.0	39.0	39.0	36.0	39.0
24 hr. I-131 uptake %	4.7	27.0	—		3.9	21.0
Protein bound iodine μgm.%	4.5	7.1	—	6.2		
Cholesterol mg.%	249.0		205.0		175.0	
17 ketosteroids mg./24 hrs.		10.0				5.1
F.S.H. mouse units/24 hrs.		>52	>13 <52	<48	<13	

laboratory findings of the patients before radiation of the hypophysis. The acid or alkaline phosphatase was elevated in all cases. One of the patients had a slight elevation of the nonprotein nitrogen and 3 patients were anemic at the time of surgery. The I-131 uptake was low in 2 of the 4 cases in which it was performed. These patients had no signs suggesting myxedema.

RESULTS

Operative Mortality. Five of the 6 patients regained consciousness after surgery. Four of these 5 had moderately severe to severe headache postoperatively which we believe may have been caused by the effects of the irradiation since it was more severe than the headache that usually occurs after hypophysectomy. Three of the 6 patients died postoperatively. It was in these patients that the pituitary stalk had been severed prior to the injection of P-32. The 3 patients who survived this procedure had not had their pituitary stalks divided. It is possible that division of the stalk in Cases 4, 5 and 6 was a factor in the postoperative mortality. Because the half-life of radioactive phosphorus is about 2 weeks it would be expected that destruction of the pituitary gland by irradiation would occur gradually. For this reason replacement of hydrocortisone was delayed in Cases 4 and 5. Recently Russell[13] has called attention to the possibility that division of the

stalk may, in itself, produce infarction of the anterior lobe of the hypophysis. The presence of fever and shock postoperatively in Cases 4 and 5 suggests the possibility that adrenal insufficiency might have resulted from sectioning of the stalk.

Patient 4 was in extremely poor condition before surgery with fever and anemia which had been corrected at another hospital. He had had a pulmonary embolus 1 week before surgery. Even though he was a poor operative risk he was operated upon because of intense generalized pain which was not relieved by large doses of narcotics.

Patient 6 had been treated previously for hypertensive cardiovascular disease. He died 32 hours after surgery. At autopsy the brain was edematous and hemorrhagic, suggesting that his hypertension may have been a factor in his death.

It is possible that more careful selection of our patients and earlier replacement of hydrocortisone would have significantly decreased our mortality with this procedure. The number of cases is too small to determine accurately what the mortality would be under more ideal conditions. In this connection Rothenberg *et al.*[11] reported only 1 postoperative death among 6 patients subjected to this procedure.

Effect of Procedure on Pituitary Function. The effect of this procedure on pituitary function is summarized in Table 2. In the 3 patients in whom less than 1.5 ml. of material was injected and in whom pituitary function could be evaluated postoperatively, there was evidence of profound depression of pituitary function. However, in Case 2 pituitary function returned to normal 7 months after surgery.

TABLE 2

Effect of intrapituitary injection of P-32 labeled chromic phosphate on pituitary function

Case No.	Stalk Divided	mc. P-32	ml. Injected	Length of Survival	Effect on Pituitary Function	Pituitary Body at Autopsy
1	No	7.2	3.0	3 mos.	No definite laboratory evidence of impairment	Minimal histologic changes
2	No	11.2	1.5	12 mos.	Severe diabetes insipidus beginning in 6th wk. lasting 5 mos. 4 wks. postop. FSH 6 mouse units/24 hrs., I-131 uptake 4.9%, urinary 17 KS 0.8 mg./24 hrs. Pituitary function returned to normal 7 mos. postop. with FSH >52 MU, I-131 9.9%, 17 KS 9.2 mg.	Minimal histologic changes in anterior lobe with focal areas of fibrosis. Posterior lobe showed glial changes
3	No	9.7	1.0	10 wks.	3 wks. postop. 24 hr. I-131 uptake 0.0%, FSH <6 MU/24 hrs. No diabetes insipidus	Very few viable cells (about 2%) in anterior lobe. Posterior lobe completely destroyed
4	Yes	10.0	1.0	5 days		No autopsy
5	Yes	10.0	1.0	5 days		Completely necrotic
6	Yes	10.0	0.5	32 hrs.		Completely necrotic

Effect of Procedure on the Cancer. Table 3 summarizes the effect of this procedure on growth of the tumor in 3 patients who survived. All of these patients had relief of pain following the injection. The roentgenograms of Case 2 showed a gradual increase in opacification during the first 5 months after the procedure, suggesting increased "blastic" activity, while the roentgenograms did not change in Cases 1 and 3. In Case 2 the serum glycoprotein[15] levels were elevated before surgery. The glycoprotein values declined to normal during the remission before returning to elevated levels when relapse occurred. The responses of the acid and alkaline phosphatase to this procedure were variable. In Case 2 the postoperative increase in the alkaline phosphatase from 66 Bodansky Units to 88 followed by a gradual fall to 29 units 4 months later together with decrease in the serum glycoprotein values strongly suggest that reduced pituitary function during this time actually caused a decrease in growth of the tumor.

In the 2 patients in whom prolonged suppression of pituitary function was achieved (Cases 2 and 3) there was definite clinical improvement. Only in Case 2 was there objective evidence of inhibition of tumor from this procedure. It is interesting to note that this patient had had only a temporary remission in his symptoms following orchiectomy and stilbestrol therapy.

Distribution of Radioactivity. In Cases 5 and 6, the radioactivity was determined in the spinal fluid and blood on the first postoperative day. In each instance approximately 0.01 per cent of the administered dose or 10 microcuries was present in the circulating blood. The radioactivity in the red cells

TABLE 3

Effect of intrapituitary P-32 on cancer of the prostate

Case No. Age	Known Duration of Cancer	Effect on Function of Anterior Lobe of Pituitary Body	Effect on Cancer				
			Length of Survival and Terminal Illness	Relief of Bone Pain	Effect on Serum Glycoprotein (gm. of Bound Hexose per 100 gm. Serum Protein)	Effect on Phosphatase Expressed as Bodansky Units	Effect on Roentgenographic Appearance of Bones
1 62 yrs.	32 mos.	No definite evidence of impairment	3 mos. Cerebral thrombosis	Complete for 10 wks.	None	Acid p. before procedure 4.8; 3 days postop. 0.7. Returned to preop. levels 2 wks. later	None
2 62 yrs.	7 mos.	Marked impairment for 6 mos. after surgery with return to normal	13 mos. Tracheitis pneumonia	Complete for 7 mos.	Gradual fall from control of 2.2 to 1.6 six mos. postop. Rise to 2.2 nine mos. postop. at time of exacerbation	Acid p. never elevated. Alk. p. showed initial rise from 66 to 88 with subsequent gradual fall to 29 four mos. postop.	Increased opacification
3 59 yrs.	27 mos.	Marked impairment within 3 wks. which persisted until death	10 wks. Pyelonephritis	Complete for 10 wks.	None	No significant change in initial levels which were 1.0 (acid) and 7.8 (alk.)	None

accounted for almost all of the radioactivity present in the blood. In both patients, the cerebrospinal fluid was bloody and contained approximately three times more radioactivity per ml. than the blood. Almost all of the radioactivity in the spinal fluid was in the red blood cells.

The concentration of radioactivity was determined at autopsy in 2 cases. In Patient 4, who died 5 days after the procedure, the necrotic pituitary tissue contained a greater concentration of radioactivity than any other body tissue. Nevertheless, this represented less than 0.1 mc. of radioactivity or less than 1 per cent of the dose administered. The concentration of radioactivity was less in the liver, but the total amount of radioactivity in this much larger organ was greater (2.5 mc.). The concentration of radioactivity per gram in the liver was approximately 4 times that in the spleen and 400 times that in the thalamus. The concentration of radioactivity in the necrotic pituitary tissue was approximately 34 times that in the hypothalamus.

In Patient 3, studied at autopsy 77 days after intrapituitary injection of P-32, a similar pattern of distribution of radioactivity was found. The greatest concentration was found in the pituitary gland but even after correction for decay the amount of radioactivity in the pituitary gland accounted for only .01 mc. of radioactivity or 0.1 per cent of the dose administered. The liver contained the equivalent of 2.7 mc. after correction for decay, or about one quarter of the administered dose. The concentration of radioactivity in the liver was approximately 3 times that in the spleen and more than 60 times that in cerebral cortex and in bone. The relative distribution of radioactivity was strikingly similar in these 2 patients.

The relative concentration of radioactivity in structures adjacent to the pituitary body was determined at autopsy in Case 3. The hypophysis had a concentration of radioactivity approximately 3 times that of the optic chiasm immediately above it, twice that of the base of the sella, 30 times that of midbrain, and 50 times that of the hypothalamus. The dura mater just behind and below the posterior clinoids contained only slightly less radioactivity than the pituitary body. This confirmed our conclusions based on preliminary studies of normal pituitary glands at autopsy which had shown that leakage of the injected dose is likely to occur posteriorly.

Since almost all of the radioactive material leaves the pituitary body within the first few days and since some of it is deposited in bones, hematologic changes might be expected in these patients. In Cases 1, 2 and 3, there was a drop in hemoglobin postoperatively in spite of transfusions. Whether this was caused by the cancer, or the radiation or other factors cannot be stated. The count of white blood cells in Case 2 dropped to 800, 7 weeks after surgery, returning to normal 9 weeks after surgery.

DISCUSSION

At the present time sufficient data have not been collected to determine the therapeutic value of destruction of the hypophysis on cancer of the prostate in patients who have experienced an exacerbation after orchiec-

tomy. It seems clear, however, that the growth of at least some prostatic carcinomas will be inhibited by destruction of the pituitary body. Whether this is caused entirely by the suppression of adrenal androgens, or whether it is caused by a reduction in growth hormone, or by other factors remains to be determined. Further study of the effects of pituitary destruction on this neoplasm is warranted.

One reason why hypophysectomy is not used more widely in cases of prostatic and breast cancer is the difficulty encountered in performing a complete removal of this gland. Because of the gland's inaccessibility, it is difficult, if not impossible, to remove the entire gland in every case. If a way could be found to destroy the pituitary body completely *in situ*, much of the technical difficulty of surgical hypophysectomy would be solved. Radiation, externally and internally applied, has been used for this purpose. More recently sectioning of the stalk with the insertion of a plate between the hypophysis and the hypothalamus has been tried in an attempt to simplify this difficult surgical procedure.[4] The direct injection of radioactive material into the pituitary body should prove advantageous if sufficient radiation is received by the gland to produce complete necrosis and if nearby structures are not damaged by this radiation.

It is well known that the normal hypophysis is quite radioresistant.[3] It has been noted by Kelly *et al.*[7] that doses of 10,000 r have resulted in no demonstrable histological changes. McCombs[9] found that over 20,000 rad was needed to produce pituitary damage and that a dose as high as 30,000 rad left viable pituitary tissue. The radioactive injection procedure of Yuhl *et al.*[16] would deliver about 10^6 rep to the gland using four pellets of Y^{90}, yet at autopsy, he found no case in which a complete destruction of the hypophysis had resulted. It is not possible for us to estimate accurately the radiation dose delivered in the procedure used by us. However, using the incomplete autopsy data from our 2 patients, we could expect a dose of between 9×10^6 and 9×10^4 rep to have been delivered to the gland. In at least 1 of our cases, this was insufficient since pituitary function returned 6 months after surgery. The radiation dose that must be delivered to produce complete destruction of the pituitary body has not yet been determined. The above data suggest that in order to produce a complete destruction of the hypophysis by irradiation a dose of 10^6 rep may be necessary.

In 3 of our patients the pituitary stalk was severed at the time of injection of the radioactive solution. In 2 of these patients no demonstrable pituitary tissue was present at autopsy. This would suggest that division of the stalk combined with irradiation may result in more complete destruction of the pituitary body than does irradiation alone. If dividing the stalk renders the anterior lobe of the pituitary body more sensitive to irradiation it is likely that this effect is ascribable to impairment of blood supply. Further work with direct injections of radioactive materials into the hypophysis might include division of the stalk in an attempt to evaluate the effect of this procedure on the radiosensitivity of the pituitary gland.

The finding of considerable amounts of P-32 in both the spinal fluid and blood as early as the first day after injection shows that this compound is rapidly disseminated throughout the body. This finding is consistent with the results of Bulkley *et al.*[2] who found that after the injection of this material into the prostate as much as 28 per cent of the injected dose may be found in the blood stream on the first day. They also found changes in bone marrow, possibly caused by irradiation, in their patients treated with chromic phosphate. However, they used a larger dose of P-32 (25–35 mc.) for this purpose than would be theoretically necessary for destruction of the hypophysis. Our finding of a low count of white blood cells in 1 of our patients 7 weeks after the injection is similar to their experience of finding a low count of white cells in 2 patients after the injection.

Because of the 3 postoperative deaths, the rapid disappearance of the radioactivity from the pituitary gland, and the failure to produce permanent interruption of pituitary function in Case 2 we do not plan to continue the use of the procedure described here. However, as pointed out above, it is possible that under more ideal circumstances the mortality rate could be reduced. It might also be possible to find ways to keep the P-32 in the hypophysis for a longer period of time thus increasing the radiation dose to the gland and decreasing the radiation of other areas. In spite of theoretical and technical advantages, the fact remains that destruction of the pituitary body by irradiation is yet to be proven superior to surgical hypophysectomy.

SUMMARY

1. Six patients with far-advanced carcinoma of the prostate gland were treated by direct injection of radioactive P-32 as colloidal chromic phosphate into the hypophysis. Five of these patients had had orchiectomy previously.

2. The 3 patients who survived the procedure noted relief of pain in bones. One of these 3 exhibited objective evidence of remission of tumor growth. Panhypopituitarism was present in 2 of these 3 patients. In 1 patient this persisted until his death 10 weeks after surgery. In the other case the hypopituitarism and diabetes insipidus produced by the procedure disappeared 6 months after surgery.

3. Autopsies were done in 5 cases. Of the 3 cases in which the pituitary stalk had not been divided, 2 exhibited only minimal histologic changes in the hypophysis. In the 2 cases in which the stalk was divided, the hypophysis was completely destroyed.

4. Evidence was obtained indicating that the injected material disappeared rapidly from the hypophysis.

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A STUDY OF THE TREATMENT OF 637 PATIENTS WITH TRIGEMINAL NEURALGIA

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(Received for publication August 20, 1957)

"Had it not been for this confounded little book which she was prone to consult at awkward moments, the operative- and case-mortality percentages for the meningiomas would have been found much lower and the end results much better. For had I been left to myself, the temptation to exclude a case here and there to improve the figures would have been irresistible. But you can't cheat in your own favor when someone else checks the record."—HARVEY CUSHING

A SERIES of 637 patients suffering from trigeminal neuralgia have been observed and treated since 1920. The symptomatology of the entire group has been studied and the various forms of therapy have been evaluated. The immediate postoperative state has been reviewed in all instances and it has been possible to assess the long-term results in 513 patients.

A total of 627 preganglionic sections of the trigeminal nerve were performed. The group of 637 patients included 373 females and 264 males. The preponderance of women sufferers, as compared to men, has been observed by others. In this series, the ratio of females to males would be even greater if the men who were seen in a large Veterans Administration Hospital were excluded.

The right face was the site of pain 393 times as compared to 228 for the left side. Sixteen patients had development of pain bilaterally but in no instance was the onset on the two sides simultaneous.

The ophthalmic division was the only division involved in only 6 instances. Three additional patients at one time had pain only in the region of the ophthalmic division, but as the disease progressed, other areas of the face ultimately became involved. Discrete maxillary involvement was seen 52 times and discrete mandibular involvement occurred 50 times. In patients who have had pain in the mandibular division, we are aware that the tongue was spared in only 1 instance. The combination of ophthalmic and maxillary pain was noted in 99 patients and the maxillary and mandibular combination was reported in 178 patients. Sparing of the maxillary division, but with pain in the areas of the ophthalmic and mandibular divisions, was recorded only twice. At least portions of all three divisions were the site of pain in 246 patients. The exact site of origin of the pain could not be determined from the clinical histories in 20 patients (Table 1).

The average age at onset for the group studied was 51 years. Our youngest patient had his first pain at the age of 15 and 1 patient and his family

TABLE 1

Distribution according to divisions of trigeminal nerve

Division	No. of Cases
Ophthalmic	6
Maxillary	52
Mandibular	50
Ophthalmic and maxillary	99
Ophthalmic and mandibular	2
Maxillary and mandibular	178
All three divisions	246
Unknown	20

maintained that there was no neuralgia involving the face until he was 89 years old. While it is generally believed that trigeminal neuralgia is not common until the 4th decade, 15 of our patients had the onset of pain before they reached their 25th year. Seven patients noted their symptoms after they were 80 years old (Table 2).

TABLE 2

Ages at onset
Average age (619 patients) 51 years

Earliest Ages at Onset		Oldest Ages at Onset	
Age (years)	No. of Cases	Age (years)	No. of Cases
15	1	89	1
16	1	85	1
17	1	83	1
18	1	81	3
19	2	80	1
21	6		
23	1		
24	1		
25	1		

Remissions of pain for long intervals are characteristic of trigeminal neuralgia. Twenty-one patients were free of pain for periods of 18 months or longer, and 2 patients were free of symptoms for 7 years (Table 3). For the most part our group of patients had their remissions in the warmer months.

Some patients had unremitting pain from the onset of the illness which did not respond to medical therapy. Frequently, surgery was advised and accepted only after several months of suffering. However, for the average, 6.4 years elapsed from the onset of pain until the patients submitted to preganglionic trigeminal section. The youngest patient operated upon was 19 years of age. The oldest patient operated upon was 93 (Table 4).

It has long been known that the incidence of trigeminal neuralgia is

TABLE 3

Duration of spontaneous remissions

Duration	No. of Cases
1½ years	6
2 years	9
2½ years	1
3 years	1
5 years	1
6 years	1
7 years	2

greater among people afflicted with multiple sclerosis than it is in the general population. Fourteen of our patients with trigeminal neuralgia also had multiple sclerosis. The neuralgia was bilateral in 1 of these patients. In 2 instances, the pain was not relieved by preganglionic section. One patient whose pain continued was later relieved by a sensory cortical resection. Another patient was free of pain for 1½ years, only to have it return for 8 years. Then, it disappeared spontaneously and has not reappeared for 6 years.

Meningiomas of the dural envelope of the Gasserian ganglion were encountered in 6 patients. Three of this group were suspected of having a paratrigeminal tumor because their pains were more continuous than is usually observed, but the other 3 had remittent lancinating pain, and there were no other clues that might lead one to suspect such a lesion.

Two patients who were operated upon for trigeminal neuralgia were later operated upon for intracranial meningiomas not in continuity with the trigeminal nerve. We do not believe that this represents more than coincidence.

One patient was known to have pernicious anemia. Three patients had positive Wassermann reactions and 3 patients had cerebrovascular accidents prior to the onset of their pain. One cannot be certain that these diseases have any bearing upon trigeminal neuralgia. We have the same impression about 2 patients who had Paget's disease of the skull, which directly affects the ease with which surgery can be performed. One patient had epileptiform seizures both prior to and following his neurotomy but the presence of an intracranial space-occupying lesion has not been verified.

The ancients believed that trigeminal neuralgia was caused by carcinoma of the antrum. We had only 1 patient with this coexistence. Herpes zoster

TABLE 4

Ages at time of surgery

Average age (620 patients)	57.4 years
Youngest patient operated upon	19 years
Oldest patient operated upon	93 years

TABLE 5

Association of trigeminal neuralgia with other diseases or symptom complexes

Disease	No. of Cases
Multiple sclerosis	14
Meningioma of dural envelope	6
Meningioma (intracranial)	2
Pernicious anemia	1
Paget's disease	2
Positive Wassermann reaction	3
Cerebrovascular accident	3
Epilepsy	1
Carcinoma of antrum	1
Herpes at onset	1

has also been implicated with the onset of trigeminal neuralgia but only 1 of our patients gave such a history (Table 5).

It has not been our practice to perform alcohol injections upon patients suffering from trigeminal neuralgia unless the pain could be relieved by local injection at the mental or infraorbital foramina. Prior to the establishment of a neurological surgery service, alcohol injections constituted the major form of therapy for trigeminal neuralgia in the Chicago area. In fact, many of the first patients in this group had been treated previously by neurologists who were recognized as technically expert in performing a variety of injection procedures. It is apparent from reviewing the records that they were eager to eliminate the more transient methods of treatment and patients were advised by them to have preganglionic section of the nerve.

We are unable to determine the exact type of alcohol injections employed in treating our patients prior to their treatment by us. But 298 people in this series had a total of 821 alcohol injections, by neurological surgeons, neurologists, general practitioners, maxillofacial surgeons, dental surgeons and others. Of 821 attempts, 503 resulted in success of varying degree. The average duration of relief obtained was 7.23 months (Table 6).

Some alcohol injections were unusually successful and deserve special comment. Fifteen patients experienced relief for 2 years. Six were free of pain for 3 years and 3 had no pain for 5 years. One was relieved for 7 years and 2

TABLE 6

Previous treatment—alcohol injections of undescribed types

Number of patients	298
Number of injections	821
Successful	503
Unsuccessful	318
Average duration of injections	4.52 months
Average duration of successful injections	7.23 months

were symptomless for 8 years. One each were free of pain for 9, 14 and 25 years.

Alcohol injections are not free of complications. The most frequent complication noted was permanent facial weakness in 4 patients. Difficulty in opening the mouth was observed in 3 patients. Two patients retained a permanent lateral rectus palsy. The following complications were observed in single instances: loss of hearing and facial weakness, transient facial weakness, paresthesias in contralateral extremities, aggravation of pain, extension of pain to an additional division, difficulty in swallowing, ulceration in the cheek and osteomyelitis of the mandible (Table 7).

TABLE 7

Complications incidental to alcohol injections

Complication	No. of Cases
Loss of hearing and facial weakness	1
Permanent facial weakness	4
Transient facial weakness	1
Lateral rectus palsy	2
Paresthesias, contralateral extremities	1
Pain aggravated	1
Extension of pain to additional division	1
Difficulty in swallowing	1
Ulceration in cheek	1
Osteomyelitis of mandible	1
Difficulty in opening mouth	3

Surgical procedures, other than preganglionic neurotomy, were utilized 13 times and these were performed prior to our seeing the patients. Two supraorbital nerve avulsions gave relief for 10 months and 2 years. Three infraorbital nerve avulsions were effective for 3 months, 11 months and 12 months. One inferior dental nerve section gave only 1 month's relief, but 4 inferior dental nerve avulsions were effective for 6 months, 15 months, 18 months and 2 years. A single patient was relieved for 30 months as a result of intracranial section of the mandibular division. Extracranial mandibular and maxillary nerve divisions were effective for 7 months in 1 patient (Table 8).

The operation utilized has been the extradural preganglionic neurotomy via the middle fossa described by Frazier and modified by Adson. The transdural route has been used only when in error, or because of its fragility and adherence to the bone, the dura mater over the temporal lobe was opened. Anesthesia has for the most part been local procaine injection. In the earlier operations, ether was used to supplement the procaine and in recent years intravenous Pentothal has been used for portions of the operative procedure. Depending upon the ability of the patient to cooperate, we have tried to have the patient awake in order to evaluate the effect of partial selective root section. Selective section has spared the sensory innervation of the eye 65

TABLE 8

Relief from operations upon peripheral nerves

Supraorbital nerve avulsion	
10 months	1
2 years	1
Infraorbital nerve avulsion	
3 months	1
11 months	1
12 months	1
Inferior dental (alveolar) nerve section	
1 month	1
Inferior dental (alveolar) nerve avulsion	
6 months	1
15 months	1
18 months	2
2 years	1
Mandibular division—intracranial section	
30 months	1
Maxillary and mandibular divisions—extracranial avulsion	
7 months	1

times. The motor root has been preserved in 206 patients. The exact status of the motor root at operation was not stated in 19 cases (Table 9).

It has been our practice to utilize the foramen spinosum as one of the major anatomic guides to the ganglion. The middle meningeal artery has been controlled, divided and its proximal end waxed into the foramen spinosum. Occasionally, we have been plagued by an artery difficult to control because of a bony prominence, previously described by one of us, which obscures the foramen spinosum and which must be removed before the artery can be coagulated and divided. The 4 operative deaths were caused by the following circumstances: one of the earliest patients operated upon by another surgeon, not an author, had profuse bleeding which necessitated packing of the wound. Subsequently, infection intervened and death resulted from meningitis. A second patient succumbed from a subdural hematoma. A

TABLE 9

Results of 627 preganglionic sections of trigeminal nerve

Operation	No. of Cases
Complete sensory section	556
Selective section	65
Details of operation unknown	4
Operation terminated without section	2
Motor root preserved	206
Exact status of motor root postoperatively unknown	19

third patient, who also had Paget's disease, died as a result of hemorrhage. The cause of death in the fourth patient was a pulmonary infarct.

Of the total group of patients operated upon we have been able to follow 513 of them continuously, and analysis of latent complications or unfavorable results is confined to a study of this group (Table 10).

The presence of transient ipsilateral facial paresis constitutes a frequent early complication (Table 11). Forty-one of our patients had facial paresis occurring either immediately after surgery or subsequently, in some instances as late as 15 days postoperatively. In some instances, recovery was complete within 1 week, but more commonly 1 month was the period required for recovery. Rarely, recovery was not complete for a year. Contralateral facial paresis was observed in 1 patient, but his recovery was prompt. Lateral rectus muscle palsy was observed in 5 patients, but fortunately was transient in each instance. Parotitis was observed only once and again this disability was transient. In many patients herpetic lesions occur after operation which are limited to the areas of the maxillary and mandibular divisions and to the lips.

There were 303 patients who had no postoperative complications or uncomfortable sequelae following section of the preganglionic trigeminal fibres (Table 10).

All patients have been taught fastidious care of the eye. This has included instruction on irrigating the eye with sterile distilled water twice daily and the use of protective shields, if the environment or occupation required it. In spite of this 39 patients have at some time had conjunctival injection and another 19 have had corneal ulceration. Of the latter, the in-

TABLE 10

Latent complications or unfavorable results in 513 patients whose postoperative follow-up has been continuous

Results	No. of Cases
No complications	303
Conjunctival injection	39
Corneal ulceration	19
Enucleation of eye	6
Nasal mucous membrane excoriation	5
Nasal ulceration	1
Scalp, nares and corneal ulceration	1
Transient loss of hearing	1
Paresthesias	
Mild	79
Severe	25
Original pain in spite of anesthesia	6
Tinnitus	2
Headache	3
Intracranial noises	1
Tearing	4
Suicide	2

TABLE 11

Complications resulting from 627 preganglionic sections of the trigeminal nerve

Complication	No. of Cases
Death	4
Facial paresis, ipsilateral	41
Facial paresis, contralateral	1
Onset—immediate to 15 days	
Recovery—1 week to 1 year	
Lateral rectus palsy	5
All recovered	
Parotitis, transient	1

jury to the eye has been so extensive as to require enucleation in 6 patients. These ocular complications were not of spontaneous origin but resulted from direct injury to the anesthetic cornea. We have not resorted to procedures such as sympathectomy because we do not believe that they occurred secondary to trophic changes. Five patients have experienced excoriation of the nasal mucosa and in 1 patient the nares became the site of a large ulceration. One patient who had difficulty in comprehending the proper care of her face had extensive ulcerations which disfigured her scalp, nares and cornea. Increasing tearing has been observed by 4 patients.

Transient loss of hearing has been observed only once, but 2 patients have complained of tinnitus for prolonged periods and many complain temporarily of fullness in the ear. One patient maintains that there are intracranial noises which were not present preoperatively. Examination of this patient fails to determine any cause for these noises and it is believed they are not ascribable to the appearance of an aneurysm or arteriovenous fistula.

Paresthesias constitute the most common postoperative subjective complaint. In 79 cases they have been classified as mild and we include in this group the sensations described as stiffness, crawling sensations under the skin and prickling sensations. Twenty-five patients complained of severe paresthesias, such as burning and deep pain. One of the patients had only mild complaints until he was given streptomycin for the treatment of pulmonary tuberculosis and since then he has complained of a severe burning sensation. Six patients maintain that they still suffer from intermittent paroxysms of pain similar to that experienced preoperatively, in spite of complete loss of sensation to pin prick, touch and temperature in the area of the trigeminal-nerve innervation.

Two patients have committed suicide, each of them 8 years after operation. One of these patients had complained of paresthesias ever since his neurotomy. The other patient was pleased with the result of his preganglionic section, but apparently could not bear the thought of suffering neuralgic pain again and when he experienced trigeminal neuralgia on the other side of his face he resorted to suicide. Of the 16 patients who had development of pain bilaterally, 2 were relieved by preganglionic section of the sensory root at

the second operation and the remainder had peripheral operations or have had long remissions.

It is our opinion that the extradural, preganglionic neurotomy as originally advocated by Frazier and Spiller, and later improved by Adson, is the most effective surgical procedure for the treatment of trigeminal neuralgia. Properly performed, the operation is an anatomical one which gives relief from excruciating pain. Properly prepared psychologically before operation for the loss of sensation which must be incurred for the permanent relief of pain, the majority of patients do not suffer from paresthesias which interfere with their lives or the peace of the surgeon. Corneal ulceration occurs only after direct trauma to an insenstive cornea and is not the result of a trophic loss, independent of injury. Facial weakness and herpes labialis which occur immediately following operation are caused by excessive and unnecessary handling of the ganglion in the latter instance, and to elevation of the dura mater from the floor of the middle fossa too far posteriorly, in the first instance.

Patients are usually confined to the hospital a week to 10 days. They are followed postoperatively at frequent intervals during the first year and annually thereafter by direct examination or by correspondence.

POSTOPERATIVE BONE CHANGES FOLLOWING LUMBAR DISC REMOVAL

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(Received for publication September 3, 1957)

SINCE the surgical technique for the removal of protruded lumbar discs has been perfected and most aspects have been standardized, many thousands of victims of sciatica have been relieved of their misery. Fortunately, serious complications of disc surgery are rare. After more than four thousand operations performed at this clinic, there have been no deaths and when infections occurred they have been superficial. In our recent survey in which the patients were followed from 1 to 20 years, 97.6 per cent stated they were benefited by operation. A commonly accepted but unexplained fact is that far too many patients complain of pain in the back and extremity for weeks and frequently months following the most simple of disc procedures. Extenuating circumstances, such as a desire for compensation and emotional factors, are probably all too often blamed in the absence of other known causes. The pain is usually not severe, improves steadily and in most instances the patient is grateful for his operation. However, we have upon five occasions among our entire group of patients encountered painful postoperative complications of such severity as to require prolonged therapy and weeks in bed. That this complication may be postoperative inflammatory disease in the lumbar disc space, as described by Turnbull,[6] has been recognized. Since the causes of osteomyelitis are multitudinous, the papers of Ghormley *et al.*,[2] Harbin and Epton,[3] Mayer,[4] Smith,[5] and Ford and Key[1] may describe this condition adequately. However, our patients did not present the clinical picture of an acute inflammatory process. They rapidly improved once the nature of their illnesses was recognized and treatment begun. Two were reoperated upon and no evidence of infection was noted. Bacteriologic studies were negative, and upon reviewing sections of tissue, no evidence of infection was discovered. The following are short summaries of these cases.

CASE REPORTS

Case 1. #299298. A.C.H., a 59-year-old white female, was seen in consultation with the late Dr. Willis C. Campbell on Feb. 29, 1940. She complained of pain low in the back with left sciatic radiation of 6 weeks' duration.

Examination. Neurologic findings were typical of a ruptured lumbar disc—spasm of muscles in the lower part of the back, extreme pain on straight leg raising, hypoesthesia and hypalgesia over the lateral aspect of leg and foot, and diminution of the

Achilles reflex. Roentgenograms of lumbosacral spine and pelvis were normal (Fig. 1A). Blood and urine were normal.

Operation (Francis Murphey). On May 19, 1940, a typical ruptured 5th lumbar disc on the left side was removed by pituitary forceps and curette.

Postoperative course was uneventful until the 5th day when excruciating pain occurred low in the back. The slightest spinal motion accentuated the pain. Large amounts of sedation were required and a body cast was applied without improvement. A daily rise in temperature to 100°–101°F. (37.8°–38.4°C.) occurred for almost 3 weeks. Repeated counts of blood cells, however, were normal.

Roentgenogram of the spine on June 17, 1940 (29 days postoperatively) disclosed a destructive lesion involving the 5th lumbar joint (Fig. 1B). The adjacent vertebral surfaces were affected by an osteolytic process.

2nd Operation (Francis Murphey). On June 24, 1940, the wound was reopened. The intervertebral space was almost empty of material and no signs of infection were encountered. Only a small amount of cartilaginous material could be removed from the intervertebral space. Biopsies were taken from the vertebral bodies.

Microscopic Examination. The biopsy material was reviewed by Dr. Frank W. Foote, Jr. There was no evidence that the lesion was inflammatory. The lesion suggested a chordoma, but no definite conclusions could be reached.

Postoperative Course. Pain continued unabated. On June 29, 1940, roentgenologic therapy (300 r) was administered to the involved spine. After three such treatments her pain ceased. A total of 1500 r was given in five treatments. She was discharged from the hospital free of pain on July 27, 1940.

Follow-Up. On Sept. 19, 1940, 4 months after her original operation, an almost complete bony fusion of the lumbosacral joint was seen on roentgen-ray examination (Fig. 1C). The patient has remained asymptomatic. When last heard from in 1954, she felt she had been benefited 100 per cent by her operations, she no longer experienced pain in the back and only occasionally was there discomfort of the extremity. She had done all of her own housework since surgery.

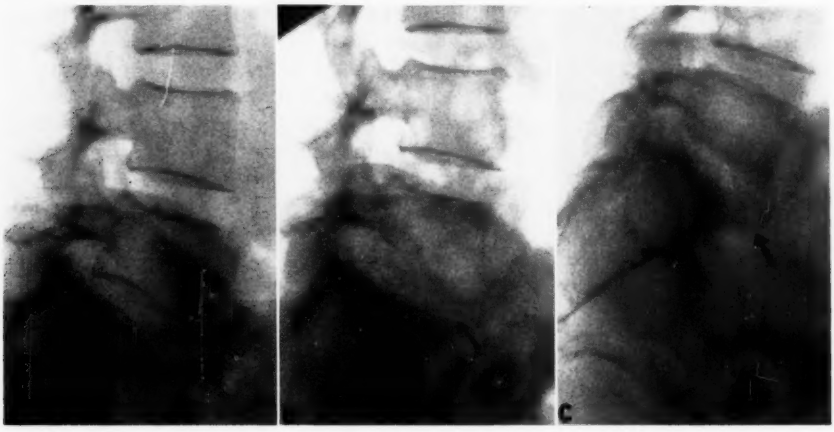

FIG. 1. *Case 1.* (A) 5-15-40. Preoperative view. (B) 6-17-40. Narrowing of lumbosacral joint space with irregularity of opposing vertebral surfaces, 1 month postoperative. (C) 9-19-40. Bony fusion of lumbosacral joint, 4 months after first operation.

Case 2. #100635. J.E.R., a 52-year-old white male, was admitted to the Baptist Memorial Hospital on Dec. 20, 1951. Ten months previously he had fallen, injuring the lower part of his back. Two weeks later right sciatic pain developed. Pain persisted despite prolonged therapy.

Examination. He walked with a marked limp. There was bilateral spasm of the paravertebral lumbar muscles. Bending was restricted. The lumbar lordotic curve was reduced. Straight leg raising on the right was painful at 150 degrees. This test on the left caused no pain. Sensation for superficial pain and touch was diminished over the 5th lumbar dermatome on the right. Both patellar reflexes were reduced. The Achilles reflexes were normal. There was narrowing of the 4th lumbar disc space seen on roentgenograms (Fig. 2A). There were no abnormalities of the urine or blood.

Operation (E. C. Schultz.). On Dec. 21, 1951, an extruded 4th lumbar disc was removed, using spinal anesthesia without difficulty. The interspace was curetted.

Postoperative course was uneventful. Penicillin, 400,000 units, was administered daily for 5 days. Because catheterization was necessary, Gantrisin (3,4-dimethyl-5-sulfanilamido-isoxazole) was administered in 1.0 gm. (15 gr.) doses three times daily for 3 days. His highest temperature was 101.2°F. (38.4°C.) on the 2nd day. At his insistence he was discharged 5 days after operation to convalesce at home.

2nd Hospitalization. One week later he returned to the hospital because of severe pain in the back, abdomen and suprapubic region which followed an upper respiratory infection accompanied by frequent coughing. He also complained of urinary frequency and dysuria.

Examination. Except for marked abdominal and particularly suprapubic tenderness, the findings were normal. The incision had healed normally. Bending was restricted by pain in the back. There was no pain in the extremity. Straight leg raising bilaterally caused marked pain in the back at 100 degrees. Reflexes and sensation were unchanged. Urine was normal. The peripheral blood contained 14,600 white blood cells, 66 per cent segmented neutrophils, 1 band cell, 29 lymphocytes, 2 monocytes and 2 eosinophils. Hemoglobin was 19.0 gm. (oxyhemoglobin method). Tem-

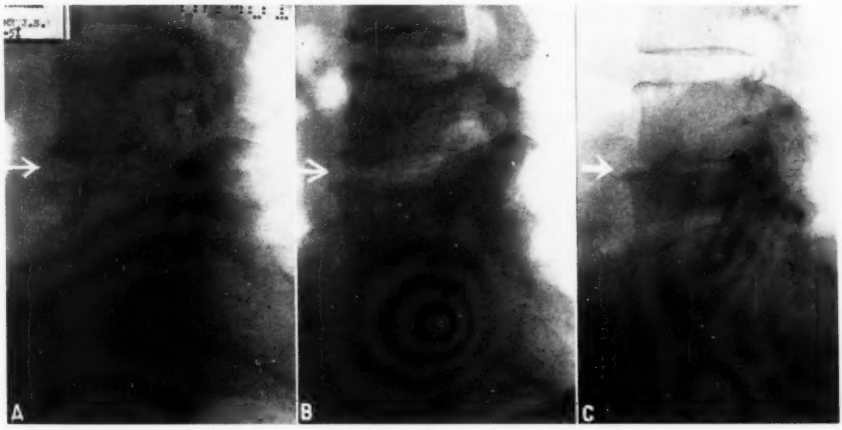

FIG. 2. *Case 2.* (A) 12-20-51. Preoperative film, showing narrowing of 4th intervertebral disc space. (B) 2-5-52. Absorption and sclerosis of bone, 6 weeks after surgery. (C) 8-4-52. Marked narrowing of 4th intervertebral space with healing by bony fusion.

perature was not above normal during these 6 days of hospitalization. Gastrointestinal and urinary tract studies revealed no abnormalities.

Course. With complete rest in bed, improvement occurred so rapidly that he was discharged on Jan. 8, 1952.

3rd Hospitalization. He was admitted on Jan. 29, 1952 because of severe pain in the groin and back. No longer was there abdominal pain.

Examination. The findings were similar to those of Jan. 2, 1952. The lumbosacral spine and pelvis were again examined by roentgen ray. Both absorption and sclerosis of bone from the opposing surfaces of L4 and L5 vertebrae were present (Fig. 2B). Because of the rarity of the case, numerous diagnostic procedures were done.

Differential blood count and two subsequent blood counts were normal. Blood urea nitrogen, carbon-dioxide combining power, sulfobromophthalein test, cephalin flocculation, sedimentation rate, alkaline and acid phosphatase determinations were normal. Spinal fluid pressure and dynamics were normal. The fluid was blood-tinged (traumatic) and its analysis, therefore, was disregarded. Lumbar myelograms were normal.

Course. On Feb. 8, 1952, a series of roentgen-ray treatments to the affected vertebrae was begun. He received a total of 900 r in six doses. Although symptomatically improved, severe pain occurred with spinal movement. For this reason a plaster spica, extending from the nipples inferiorly to both knees, was applied. All pain ceased by Feb. 24, 1952, and he was discharged 5 days later. The spica was removed 2 months thereafter.

Follow-Up. Roentgenography in August 1952 showed a solidly healed fusion between the 4th and 5th lumbar bodies with obliteration of the joint space (Fig. 2C). This has been followed by frequent radiologic examinations for the past several years. He has remained asymptomatic.

Case 3. #108045. S.S., a 24-year-old white female, was seen in consultation with Dr. Alvin Ingram on Oct. 8, 1951. She had always been in good health until the onset of acute pain low in the back on Sept. 6, 1951, followed 2 days later by left sciatic pain. Rest in bed and traction were valueless.

Examination. The pertinent findings were marked spasm of the paravertebral muscles, restricted movement of the lumbar spine, pain on straight leg raising, decreased sensation to touch and pin prick over the lateral aspect of the foot, and a reduced Achilles reflex.

Roentgenogram of the lumbar spine was normal except for the presence of a lumbarized 1st sacral vertebra (Fig. 3A). Blood and urine were normal.

Operation (R. L. DeSaussure). On Oct. 10, 1951, under spinal anesthesia, an extruded lumbar disc was removed from the 5th lumbar interspace by curette and pituitary forceps.

Postoperative course was uncomplicated. The highest temperature recorded was 100.6°F. (38°C.) on the 2nd day. Penicillin, 400,000 units S.R., was administered daily for 5 days. She returned to her home on the 7th postoperative day.

When she was seen again on Nov. 9, 1951, she felt improved but slight pain persisted in the left hip. A marked right lumbar scoliosis had developed. Straight leg raising was painful on the left at 135 degrees. The Achilles reflex on the left was absent. She was permitted to return to work as a stenographer and exercises for the back were advised.

Early in March 1952, 5 months after surgery, more intense pain occurred. Results of examination on March 7 were similar to those of November except that she no longer had pain in the extremity. Complete rest on a firm bed was prescribed. The pain in the back became progressively worse and pain returned to the left lower extremity.

2nd Hospitalization. She was readmitted on April 4, 1952, at which time there was pain in the lower part of the back, both lower extremities and left groin. Any movement accentuated the pain.

Examination. The lumbar lordotic curve was increased. There was marked spasm of the paravertebral muscles. There was no spinal or paraspinal tenderness on pressure. Objective weakness could not be elicited. The remaining findings were similar

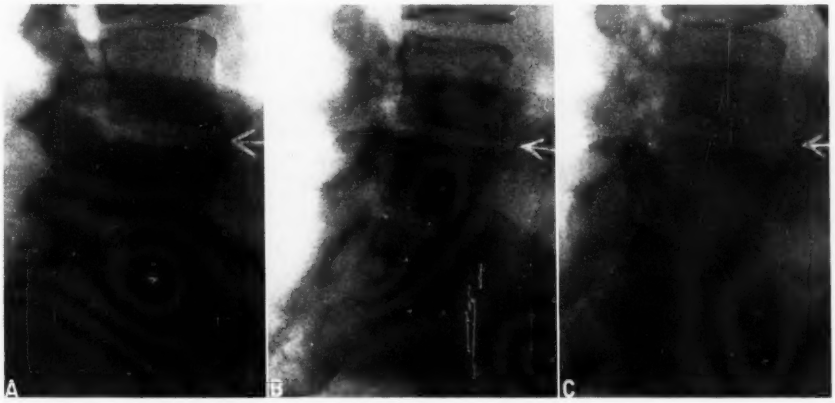

FIG. 3. *Case 3.* (A) 9-29-51. Preoperative roentgenogram. (B) 4-4-52. Narrowing of 4th intervertebral disc space with sclerosis and absorption of the adjacent vertebrae, 6 months postoperative. (C) 9-10-55. Complete restitution of bone with preservation of 4th intervertebral space, 4 years after operation.

to those on previous examinations. During the 7 days she was in the hospital there was no elevation of temperature.

Sedimentation rate 21 mm. in 1 hour, count of white blood cells was 7,000 with 61 per cent segmented neutrophils, 29 per cent lymphocytes, 8 monocytes and 2 eosinophils.

In roentgenograms of the lumbar spine the superior margins of the lumbarized sacral vertebra appeared ragged and irregular. The lesion was ascribed to interference with the vascularity of the vertebrae. An infection could not be excluded (Fig. 3B).

Course. Three million units of penicillin were administered and roentgen-ray therapy to the lower lumbar spine was carried out. She received 800 r in four doses. She was discharged asymptomatic on April 11, 1952. Complete rest in bed at home was carried out for 8 weeks, during which time no antibiotics were administered.

Follow-Up. She has been completely free of pain since the last hospitalization. There were no abnormalities on examination on Sept. 12, 1955. Roentgenograms of the lumbar spine showed normal-appearing intervertebral spaces without narrowing or evidence of the previous bony changes of the adjacent vertebrae (Fig. 3C).

Case 4. #187514. L.T., a 43-year-old housewife, was seen on May 12, 1955. She had complained of intermittent pain low in the back and right sciatic pain for years. For 4 months no relief was derived from medication and confinement to bed was necessary.

Examination. She walked with a limp favoring the right extremity. The lumbar lordotic curve was decreased and there was a lumbar scoliosis to the left. Marked spasm of the paravertebral muscles was present. Straight leg raising was positive at 150 degrees on the right and negative on the left. There was no muscular weakness. Slight atrophy of the right calf was noted. Sensation for pin prick and touch was diminished over the lateral aspect of the right foot. The Achilles reflex was absent on the right. The remaining reflexes of the lower extremities were normal.

Roentgenograms of the lumbar spine showed a reduction in the lordotic curve, a left scoliosis, and narrowing of the 5th intervertebral disc space (Fig. 4A). The temperature was normal. Blood and urine were normal.

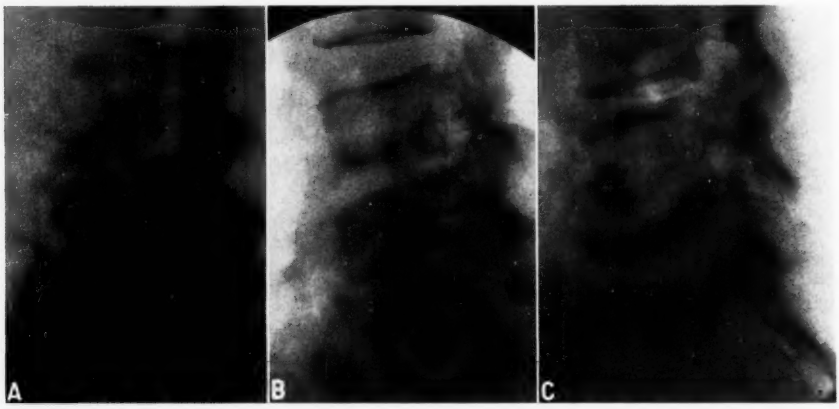

FIG. 4. *Case 4.* (A) 5-12-55. Preoperative roentgenogram. (B) 7-3-55. Destruction of bone at 4th lumbar interspace, 7 weeks postoperative. (C) 1-30-56. Narrowing of 4th intervertebral space with bony fusion, 8½ months postoperative. The 5th lumbar body is markedly narrowed.

Operation (E. C. Schultz). On May 14, 1955, under spinal anesthesia, an extruded 5th lumbar disc and a ruptured 4th lumbar disc were removed. The intervertebral spaces were curetted.

Pathologic report was "fibrocartilage with degeneration."

Postoperative course was uneventful. The highest temperature was 101.2°F. (38.4°C.) on the 1st day. Penicillin, 400,000 units, was administered for 4 days. She was discharged free of pain on May 22, 1955.

2nd Hospitalization. Seven weeks later, on July 2, 1955, she was readmitted with a history of progressively severe pain in the lower part of the back and pain in the right thigh on attempting to sit or walk. Pain was noted on her return home from the hospital. She had remained in bed most of the time and she appeared weak and anemic.

Examination. The temperature was normal. The operative wound was well healed. Standing was impossible because of the severe pain in the back and groin it

produced. Severe spasm of the paravertebral muscles existed and no movement of the lumbar spine was observed. Straight leg raising was now bilaterally positive at 150 degrees, causing pain in the right hip. The remainder of the findings were similar to the original.

Peripheral blood and urine were normal. Alkaline phosphatase and sedimentation rate were normal. No ova or parasites were found on examination of the stools.

Roentgengograms showed that the lumbar spine was straightened, and the 4th lumbar interspace was narrowed. Destruction of the end plates and adjacent bone of the inferior portion of the 4th body and the superior portion of the 5th body was evident (Fig. 4B). These changes suggested tuberculosis to the roentgenologist.

2nd Operation (E. C. Schultz). The old operative wound was reopened on July 7, 1955, using Pentothal anesthesia. The 4th interspace was found to contain very soft slimy-appearing cartilage. No fluid or pus was encountered. The annulus was stripped away with ease so that a very large quantity of cartilage was removed. A roentgenogram made at the operating table confirmed this to be the 4th lumbar interspace.

Pathologic Report. Dr. Merlin L. Trumbull reported, "The disc tissue itself departs from the usual appearance of herniated discs by having scattered small foci of polymorphonuclear cells. Some of these have pyknotic nuclei. One could term this a mild form of acute nonspecific chondritis. The presence of polymorphonuclear leucocytes, lymphocytes and plasma cells about the few bone fragments submitted suggests a subacute osteomyelitis. There is no significant necrosis of bone demonstrated."

Postoperative Course. The patient complained of more pain than following her first operation. There was a slight rise in temperature daily to around 100°F. (37.8°C.). Smears and tissue cultures made of the material removed from the 4th intervertebral space were negative. Because of previous success in control of pain, roentgen-ray therapy was administered to the involved spine in doses of 200 r daily for 5 days. Following the third treatment pain decreased markedly. She was discharged on July 22, 1955, to remain in bed at home for 2 weeks.

Follow-Up. When last examined on Jan. 30, 1956, she was free of pain. There was roentgen-ray evidence of fusion of the 4th and 5 lumbar bodies (Fig. 4C).

Case 5. #196741. M.A.W., a 34-year-old housewife, was operated upon in February 1953 in New Orleans, Louisiana and the 4th and 5th lumbar discs were removed from the left side. Postoperative course was uneventful. Six months later the pain recurred and myelography was done in February 1955. Re-operation was performed in Monroe, Louisiana in February 1955, and tissue was removed from the 4th and 5th interspaces on the left. Again a normal recovery ensued for 5 weeks. Then severe pain in the back and both lower extremities recurred. Because of pain, she was unable to walk. Any movement of the lumbar spine exaggerated her pain. She remained in bed 5 weeks and her activity was restricted for an additional month. Pain continued and she was seen in consultation by Dr. R. E. Semmes. Because of persistent symptoms that incapacitated her, re-operation was advised.

Examination. Roentgenograms of the lumbar spine made Sept. 14, 1955, were reviewed. There was narrowing of both the 4th and 5th intervertebral spaces. There was sclerosis of the adjacent bony surfaces of the 5th interspace (Fig. 5A).

Operation (R. E. Semmes). On Sept. 17, 1955, partial hemilaminectomy at L4 and hemilaminectomy at L5 was performed. The 5th lumbar and 1st sacral nerve

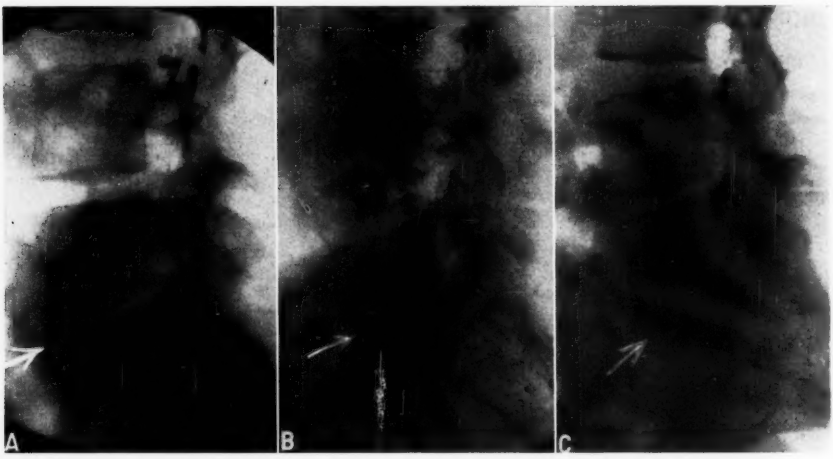

FIG. 5. *Case 5.* (A) 9-14-55. Appearance of lumbar spine after 2 operations and a myelogram. L5 interspace is narrowed. (B) 1-6-56. Absorption and sclerosis of bone appears at L5 interspace, 3½ months after 3rd operation. Interspace was not entered at surgery. (C) 10-13-56. Further narrowing of joint space has occurred and bony fusion is evident, 13 months postoperative.

roots were dissected from dense scar tissue. The intervertebral spaces were not entered.

Postoperative Course. She did well following operation and returned to light work 1 month later. During the first week in November, 7 weeks after surgery, pain occurred in the sacral region and in both hips. Spinal movement or straining accentuated the pain. Analgesics were necessary even though she was confined to bed.

When re-examined Jan. 6, 1956, there was paravertebral spasm and bending was restricted. Pressure over L4 and L5 spines produced pain located in the sacrum. Motor power, sensation and reflexes were normal. Straight leg raising was painless. Rotation of either hip produced low-back pain. Motion of the spine was guarded since even turning on the examining table was accompanied by severe spasm of the muscles of the back. Compressing the veins of the neck, however, was painless.

Roentgenograms of the lumbar spine showed loss of cortical detail, absorption of bone, and reactive sclerosis of the opposing surfaces of L5 and S1 vertebral bodies (Fig. 5B).

On Jan. 7, 1956, and again on Jan. 9, 1956, roentgen-ray therapy was administered to the lumbosacral joint, consisting of 200 r at each treatment. An additional 600 r units were given in three doses of 200 r each at another hospital. Subjective relief from pain resulted.

Follow-Up. She was last seen here on Oct. 22, 1956. She was markedly improved and almost completely free of discomfort.

Roentgenograms of the lumbar spine demonstrated pronounced narrowing of the 5th intervertebral disc space and the adjacent surfaces of the sacrum and 5th lumbar body were sclerotic (Fig. 5C).

Case 6. #426084. An additional case was encountered by Dr. R. E. Semmes on the Neurosurgical Service of Dr. Paul Bucy of Chicago. Dr. Bucy has kindly permitted us to include his patient.

W.C., a 32-year-old white male, was referred to the Neurosurgical Service of the Chicago Wesley Memorial Hospital on March 11, 1956 by Dr. R. Hilker. The patient stated that in 1948 he may have injured his back playing baseball and had suffered intermittent pain in the lumbar area. In November 1955, without any known injury, his condition became worse and for the first time there developed radiation of pain into his right leg, followed by weakness of dorsiflexion of the right foot. In January 1956, a myelogram was done. There was a filling defect at L4 level on the right.

On Jan. 6, 1956, right hemilaminectomy was performed by an orthopedic surgeon. Herniated disc material and other loose material were removed from the 4th lumbar interspace. The interspace between the vertebral bodies was not curetted.

Following operation the sciatic pain was relieved and some strength returned to his right foot. Three weeks later he began to complain of severe pain in the lower part of the back with development of severe spasm of paravertebral muscles. He was treated by rest in bed and traction, with improvement. He was unable to bear his weight either sitting or standing because of pain in the lumbar region.

Examination. The patient was a well developed, well nourished, alert and cooperative man. His blood pressure was 118/60, pulse rate 88, respiratory rate 16, and temperature 98.6°F. There was a well healed midline lumbar scar. No spasm of muscles was present as he lay quietly in bed. There was no particular tenderness to percussion except at the level of the 5th lumbar vertebra. Reflexes were symmetrical though not brisk in the lower extremities, with the exception of the right Achilles reflex which was decreased. Strength was normal in the lower extremities. Kernig's sign was positive bilaterally producing pain in the lumbar region. The patient was unable to stand or sit without severe pain. There was no sensory change. No atrophy was demonstrated in the lower extremities.

There was a normal hematocrit of 44 per cent, and count of white blood cells was 5,900 with 46 per cent polymorphonuclear leucocytes, 48 per cent lymphocytes, 5 per cent monocytes and 1 eosinophil. Sedimentation rate was 24 mm. per hour and 26 mm. per hour on two occasions. The Kahn test was negative. Urinalysis was negative. The nonprotein nitrogen was 16.2 mg. per cent.

Roentgenograms of the thoracic and lumbar spine were made. There was a partial laminectomy on the right side at the 4th and 5th lumbar vertebrae and some residual Pantopaque in the subarachnoid space. On laminagrams of the lumbar spine there was definite evidence of destruction of the cortical surface of the inferior margin of the body of the 4th and superior surface of the body of the 5th lumbar vertebrae without collapse of the intervertebral space or of either body.

Course. During his hospitalization of 21 days there was no fever and he was given roentgen-ray therapy in four treatments of 200 r each to the skin every 3rd day. This treatment delivered a total of 800 r to the skin or a calculated 370 r to the 4th lumbar interspace. He continued to complain of severe pain in the back and was confined to rest on a firm bed. At his discharge the patient admitted that the pain was somewhat better though still quite severe.

A second laminagram was made 13 days after the first. There was little change.

Follow-Up. The pain diminished and he returned to work about 7 weeks after leaving the hospital, though using a cane. He was able to work full time and to walk normally 2 months after discharge.

The patient was seen in the office on Nov. 26, 1956. He was feeling well and had no complaints. He was wearing a brace more for protection than for any other reason.

He believed that when the brace was removed he felt weak and tired. Neurologic findings were all normal.

Roentgenograms of the lumbar spine showed a sclerosing type of reaction of the subarticular bone of the opposing surfaces of the 4th and 5th lumbar vertebrae.

A laminagram on Dec. 5, 1956 demonstrated a dense sclerosis of the opposing surfaces of the 4th and 5th lumbar vertebrae with narrowing of the interspace between the 4th and 5th vertebrae. The urine contained no alkaptone.

The patient was last seen on Feb. 26, 1957. He was feeling well but used his brace occasionally. He had no complaints. Neurologic findings were completely negative.

DISCUSSION

The literature of the past twenty-five years has been reviewed and no concise report of the aforementioned complications of disc surgery was encountered. It is our belief the complication is not infrequent but is often overlooked. In none of our cases were there the usual signs of infection postoperatively. One patient had severe pain 5 days after surgery requiring treatment, a second had symptoms by the 12th day, while 5 months were required by the third, 7 weeks by the fourth, about 3 months by the fifth and 3 weeks by the sixth before medical treatment was sought. In all, we have been particularly impressed with the severe pain in the back and spasm of muscles. The pain is mechanical in nature and movement of the back greatly accentuates pain. Because of marked abdominal pain in 3 of our patients, the possibility of intra-abdominal pathology was considered. Large amounts of anodynes were necessary for symptomatic relief. Recalling other patients with prolonged symptoms postoperatively, we cannot help but believe a number of similar cases have been overlooked. It seems logical to assume that with various degrees of involvement of joints, only the most severe cases have come to our attention. It has been our constant concern that such patients with few objective findings and severe pain may be neglected or completely misjudged. Although we have no evidence that the pathologic process is a septic one, the roentgen-ray studies are suggestive of this. Tissue from Case 4 was examined and compared with disc material removed from patients having recurrent ruptured lumbar discs without finding any significant microscopic differences. Routine roentgenograms of the spine often are inadequate to demonstrate early lesions and laminagraphy will then prove valuable as in Case 6.

In a recent discussion of this paper with Dr. Albert D'Errico, recalling a similar case of his own, he suggested virus infection as the possible etiology. The role of surgical trauma to the joint space seemed likely as a cause but in our Case 5, bone absorption occurred at an interspace which had not been entered. Two neurosurgeons have informed me of cases of their own in which the affected lumbar interspace was distant from the one subjected to operation. This would negate local trauma to the adjacent vertebral bodies as essential to the production of the changes in the bone seen on roentgenograms.

Believing the lesions may be of a type of aseptic necrosis or "osteochondritis," roentgen-ray therapy was tried in the hope of obtaining relief of pain as sometimes results in similar conditions (osteitis pubis, osteitis of the tibial tubercle). The results were gratifying. All our patients had relief from irradiation, with time and rest. I have learned that in similar cases the patients responded equally well to the administration of cortisone.

SUMMARY

A complication of disc surgery is discussed. It most probably occurs far more frequently than we now suspect. Only with further investigation will a clearer understanding of this complication ensue and better methods of diagnosis and treatment occur.

ADDENDUM

Since completion of this paper another patient with a similar lesion was seen by the author. This was a medicolegal problem in which the lesion had gone unrecognized and untreated for months and the patient was suspected of grossly exaggerating his disability. Roentgenographic changes were marked. He responded readily to treatment.

Recently we were asked to see still another patient with recurrent severe spasm of the muscles of the lower part of the back which began 3 weeks after removal of his 5th lumbar disc from the left side. Spasm had persisted 3 months. He was confined to bed by the pain and large amounts of analgesics were required. Roentgenograms of the spine were normal. On laminagrams bone absorption and condensation were readily apparent on the left side of the 5th interspace. Response to treatment was prompt.

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A NEW THEORY ON THE DYNAMICS OF BRAIN CONCUSSION AND BRAIN INJURY*

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(Received for publication September 9, 1957)

IN THE design and evaluation of protective headgear, there is need for the establishment of physical criteria upon which the performance of helmets subjected to impact can be determined. In the present state of the protective helmet art, there is little agreement regarding either the significant parameters to be measured or their critical threshold values. It is agreed, however, that the primary function of the helmet is to provide protection from brain concussion in case of accidental impact to the head. An extensive search of the literature has revealed theories relating to the mechanism of brain concussion and brain injury by Gama,[6] Duret,[5] Miles,[10] Russell,[12] Munro,[11] Goggio,[7] Denny-Brown and Russell,[4] Courville,[2] Gurdjian and Webster,[8] Holbourn,[9] Walker, Kollros and Case,[13] Ward, Montgomery and Clark[14] and others. None of these theories, however, was found to be sufficiently comprehensive to enable the establishment of the desired criteria. An excellent review of the development of the current knowledge of brain concussion has been presented by Denny-Brown.[3]

If it can be established that brain concussion is produced by, or occurs simultaneously with, a specific detectable physical phenomenon occurring within the head, it then may be possible to obtain considerable information on the threshold of concussion from research on impact on human cadavers. The data from such research could then be used to establish a standardized set of laboratory test conditions for the evaluation of helmets subjected to impact.

The subject of brain concussion is normally the exclusive concern of those in the medical profession. Research in the field of brain concussion has, in the past, accordingly been conducted mainly by those trained in the field of medicine. It must be recognized, however, that research dealing with impact to the head involves engineering dynamics, a highly specialized field that is normally foreign to the medical researcher. Lack of a clear understanding of the dynamics involved in impact to the head has served as a considerable handicap to these researchers.

The basic purpose of this research effort has been to investigate the dynamics of the head and its contents when subject to impact. The actual experimentation involved was limited to the study of the dynamics of fluid-filled glass flasks simulating the human head. Although the medical literature

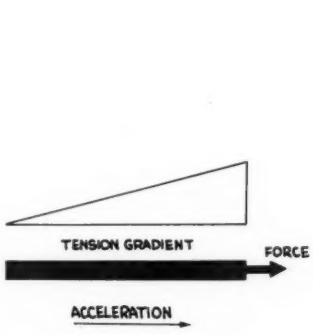
* Initially presented to a selected group of Aero-Medical Naval Personnel at the Aero-Medical Convention in Washington, D. C., on March 18, 1952.

on brain concussion was carefully reviewed for guidance of this study, the actual research was of an engineering nature, conducted by engineering personnel.

BASIC DYNAMIC CONSIDERATIONS

Since this is a problem in dynamics let us start with Newton's first law of motion: Force equals mass times acceleration.

If we take the simple case of a bar being accelerated from one end by a tension force, as shown in Fig. 1, we shall find that the distribution of tensile force in the bar will be maximum at the end the tensile force is being applied, graduating to zero at the other end. The tension at any point along the bar will be proportional to the remaining mass being accelerated.



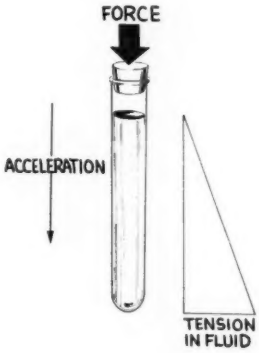


FIG. 1 (*left*). Tensile stress gradient in a bar being accelerated by a force at one end.
FIG. 2 (*right*). Tensile stress gradient developed in the fluid, contained in a simple test tube, because of the downward acceleration of the tube produced by impact to the top of the tube.

Let us now take a similar case in which tension is developed in a fluid, as shown in Fig. 2. If a glass tube partially filled with a fluid is struck on the top, the fluid will be accelerated downward by the tensile force developed in the fluid itself. The distribution of the tensile force in the column of fluid will be proportional to the mass of fluid above the level considered, being maximum at the bottom and zero at the surface of the fluid. If the tube is given a sufficiently hard blow so that the tensile force exceeds the tensile strength of the fluid, the fluid will tear apart, producing temporary cavities. Since the maximum tensile force is developed at the base of the fluid column, failure of tension or cavitation can be expected at this point. This phenomenon is demonstrated in Fig. 3.

Let us now take the case in which the glass tube is sealed at both ends and completely filled with a fluid as shown in Fig. 4. Neglecting radial expansion of the tube and assuming the compressibility of the fluid to be greater than the compressibility of glass, we can conclude that the fluid

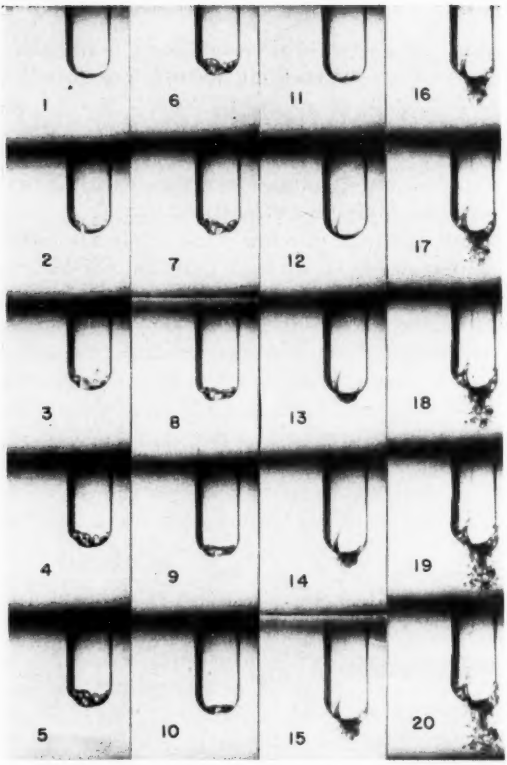
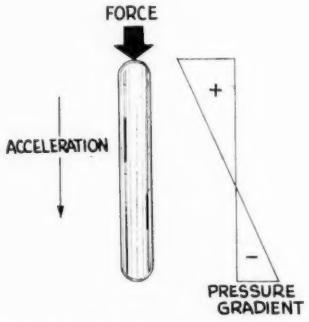


FIG. 3. High-speed photographs (4,000 frames per second) of an ordinary glass test tube, partially filled with water, being impacted from the top. Failure of tension of the fluid occurs at the base of the tube in frame 2. Final collapse of the cavity formed occurs in frame 12. The impacting force produced by the collapse of the cavity then fractures the base of the tube.



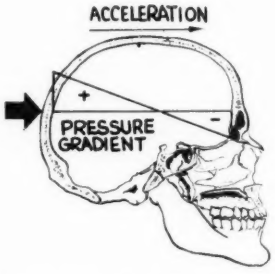


FIG. 4 (*left*). Tensile stress gradient developed in the fluid contained in a closed tube because of acceleration produced by impact to one end.

FIG. 5 (*right*). Tensile stress gradient developed in the fluid of the brain because of acceleration produced by impact.

column will be accelerated by both pressure from the impacted end of the tube and tension from the opposite end of the tube.

Although the human skull is much more complex than the simple case stated above, there is reason to believe that distribution of pressure upon impact of the unrestrained head is of the same nature. For lack of substantiating evidence, let us assume that the distribution of pressure within the unrestrained skull upon blunt impact graduates from a positive pressure on the impacted side to a negative pressure on the opposite side, as shown in Fig. 5. This differs from the case in which the head is restrained and the forces are of a crushing nature.

TENSION FAILURE OF FLUIDS

If we are to assume that zones of negative pressure develop within the head upon impact, we then can conclude that cavities can develop within the fluid in the head, providing the negative pressure is sufficiently great to produce tension failure of the fluid.

The magnitude of the negative pressure required to produce tension failure is dependent on the following three factors: (1) Ambient pressure. (2) Vapor pressure of fluid. (3) Cohesive strength of the fluid.

Normal fluids, other than those specially treated in the laboratory, have little or no cohesive strength because of the presence of gas nuclei and other contaminants.

If we assume zero cohesive strength, we can then consider the fluid being held together by the external atmospheric pressure. If this pressure is removed (14.7 p.s.i. at sea level), cavities will immediately form because of the vapor pressure of the fluid.

MECHANISM OF TISSUE DAMAGE

In the various theories that are based on fluctuations of pressure it is generally concluded that it is the negative phase of the pressure cycle that is causing the tissue damage. It has been most difficult to visualize just how the application of a uniform field of negative pressure could produce brain damage of a focal nature. It is apparent that some significant factor is being overlooked.

If we assume formation of cavities within the brain caused by acceleration of the head, upon cessation of the accelerative force the cavities will collapse immediately because of the ambient pressure and the surface tension of the fluid.

The mechanical violence of collapsing cavities has long been known to the engineering profession. The first practical problems of cavitation came with the introduction of rotary hydraulic apparatus, such as ship's propellers and centrifugal pumps. If a propeller or pump rotor is driven too hard, cavities will form on the low pressure side of the blades because of tension failure of the fluid. The violent collapse of these cavities causes the metal to become spongy and wear away. This process is known as cavitation erosion

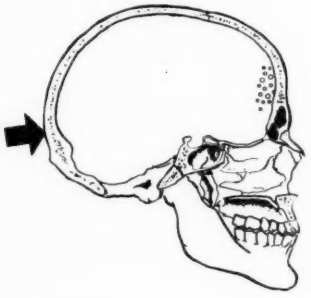
and has been the subject of many investigations. It is generally agreed that the erosion is caused by the impacting force of the collapsing cavity exceeding the strength of the metal or at least the fatigue strength. The impacting pressure produced by the collapsing cavities is believed to be in the order of 30,000 atmospheres. If the cavity were empty and the medium incompressible the force of collapse would be infinite.

The mechanism of brain concussion being proposed is based on the premise that the various forms of focal brain damage are the result of the violent collapse of cavities formed within the brain.

CONTRECOUP CAVITATION

On the basis of the assumption made in relation to the distribution of pressure, a plausible explanation for the phenomenon of contrecoup becomes apparent. If the zone of negative pressure, which is opposite the point of impact, exceeds the sum of the cohesive pressure and the ambient pressure, cavitation will occur as shown in Fig. 6. The location of the cavities will be dependent on the actual distribution of pressure and the location of the gas nuclei. The maximum size of the cavities will be dependent on the magnitude of the negative pressure and its duration above the threshold of cavitation. Once the negative pressure falls below the threshold necessary to support the cavities, the sequence of collapse begins.

It is this violent collapse of these cavities (Fig. 7) with the associated impacting pressures that produce the physiological damage recognized as contrecoup. If a large number of small cavities are formed, the damage will show as a number of small petechial hemorrhages where the individual cavities formed and collapsed; however, if the cavitation is localized at one point on the surface of the brain, the characteristic conical contusion with the apex extending into the brain will result. If the collapse of the cavity were sufficiently intense, it is conceivable that contrecoup fracture could occur.



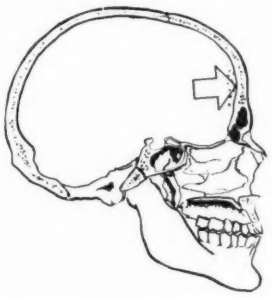


FIG. 6 (*left*). Contrecoup cavitation occurring at a point opposite the impact because of tension failure of the fluid.

FIG. 7 (*right*). Contrecoup brain injury of a focal nature resulting from the violent collapse of the cavities formed during the interval of acceleration.

Some explanation is necessary for the relative resistance of the head to contrecoup injury from frontal blows. Cases reported involve a large percentage of fatal automobile accidents. In accidents of this nature, it is reasonable to assume (for the frontal impact) that the head is inclined somewhat forward as shown in Fig. 8. This position of impact places the foramen magnum adjacent to the area of negative pressure. It is possible that the feeding action of fluid through the foramen magnum is sufficient to attenuate the peaks of negative pressure, thereby tending to prevent contrecoup cavitation, for this particular type of impact.

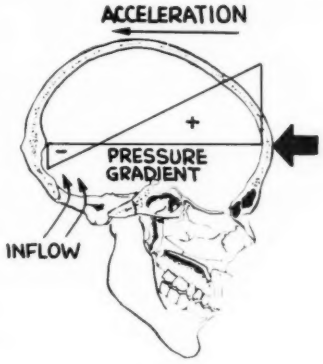


FIG. 8. Inflow effect through foramen magnum attenuating negative pressures for frontal impact.

COUP CAVITATION

Damage of a focal nature occurring in the area immediately adjacent to the blow can be explained in the following manner: A sharp nonpenetrating blow to the skull (Fig. 9) will produce the distribution of negative-positive pressure discussed above as long as the force of impact and acceleration of the head are maintained. Upon cessation of the impacting force there is no longer the acceleration of the head essential to support this distribution of pressure.

At the instant of the collapse of the field of pressure because of cessation of the acceleration, the skull is left locally depressed as a result of the force of the blow. If fracture does not occur, the elasticity of the skull will cause a very rapid recovery of shape at the point of depression. The elastic forces in the skull returning the depression to its original shape can be sufficiently high to cause localized negative pressure sufficient to cause tension failure, within the fluid. Coup injury, therefore, frequently shows not only the contusions associated with direct impact but also shows the petechial hemorrhages caused by subsequent coup cavitation.

DIFFUSE BRAIN DAMAGE

The above mechanisms of coup cavitation and contrecoup cavitation relate to damage of a focal nature found near the surface of the brain. These mechanisms fail to explain the cause of diffuse contusions found throughout the brain. It is apparent that an additional mechanism is required to extend the damage into the central portion of the brain.

RESONANCE CAVITATION

After many months of futile experimentation on the dynamics of fluids, the author observed the unusual occurrence shown in Fig. 10. The photo-

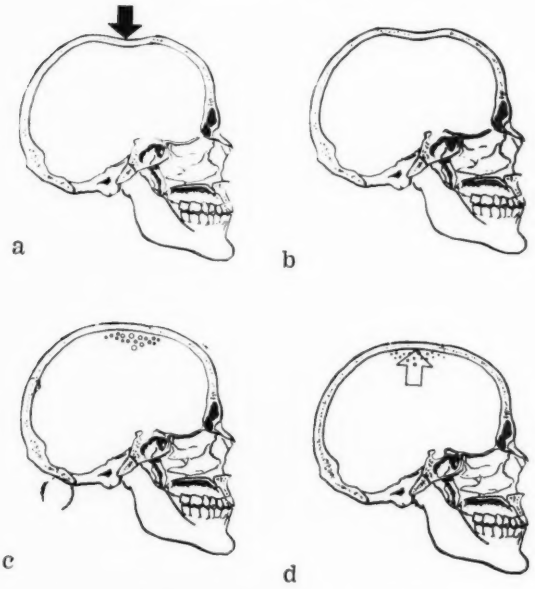


FIG. 9. Mechanism of coup cavitation. (a) Impact to top of skull causes local deformation of the skull inward. (b) Cessation of the impacting force leaves the skull locally deformed in a highly stressed condition. (c) Snap-back of the deformed skull to its normal position results in localized cavitation. (d) Collapse of the cavities formed produces the punctate contusions associated with coup injury.

graphs, taken at approximately 4,000 frames per second, are of a simple glass test tube partially filled with water. The tube is being impacted from the top with a hammer.

Normally the photographs of this experiment had shown the cavities to form at the bottom of the tube and then collapse without any subsequent formation of cavities.

In the particular experiment shown, however, there was apparently a small bubble of gas adhering to the side of the tube. As the negative pressure developed because of the impacting force, this bubble expanded and cavity formation at the base of the tube did not occur. Upon collapse of this cavity, however, the tube was apparently driven into radial oscillation resulting in subsequent spontaneous cavitation of a disperse nature.

Radial oscillation of such a tube will cause a corresponding fluctuation of the internal volume of the tube. Such a radial oscillation at low frequencies will merely result in an oscillation of the height of the fluid column. If the amplitude and frequency of the oscillation are sufficiently high, negative pressures will be developed on the expanding phase of the cycle that will produce cavitation.

To extend this experiment to one more closely simulating a human skull,

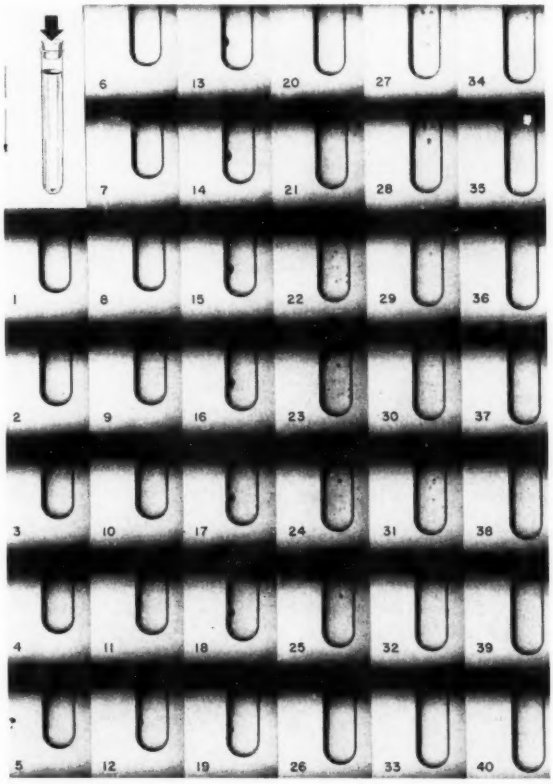


FIG. 10. High-speed photographs (4,000 frames per second) of an ordinary glass test tube, partially filled with water, being impacted from the top. Frame 12 shows the growth of a gas bubble on the side of the tube, precluding the normal formation of the cavity at the base of the tube. Collapse of this cavity in frame 20 then drives the tube into radial oscillation resulting in the resonance cavitation shown.

a common 2,000 ml. glass flask filled with water was used as shown in Fig. 11. The stopper was grooved at the sides to vent the space above liquid to atmosphere. The flask was impacted by striking the rubber stopper a sharp blow with a rubber mallet. The results of this experiment are shown in Fig. 12.

If you will observe the photographs carefully, you can see the formation of the contrecoup cavities with their subsequent collapse followed by several cycles of resonance cavitation. You can also observe that in resonance cavitation there is the recurrence of the cavities at the same distinct points, resulting in multiple impacts at these points. Not only does the collapse of the initial cavity produce extremely high force of impact, but in resonance cavitation this impact is repeated at the same points.

Evidence obtained by strain-gage instrumentation of the flask indicates

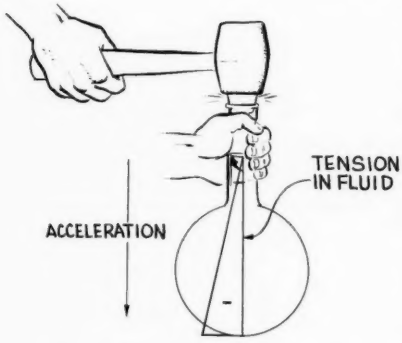


FIG. 11. Tensile stress gradient developed in a spherical flask because of the downward acceleration produced by impact to the top of the flask.

that the significant oscillatory mode in this phenomenon is radial in nature, producing large fluctuations in internal volume of the flask. Knowledge of the exact nature of the oscillatory mode is not essential to this theory as various modes of oscillation could produce volumetric pulsations. Considering a cycle of resonance of the human skull, the pressure within the skull would increase as the volume of the skull decreases, and, conversely, the pressure within the skull would decrease as the volume of the skull increases. Because of this fluctuation of volume, there would be a pumping action through the foramen magnum and other cranial cavities, but their effect on the overall pattern of pressure would be limited because of the inertial properties of the fluid. If the magnitude of the oscillation were sufficiently great, disperse cavitation would occur on the expanding phase of the cycle (Fig. 13). As the distribution of pressure under this oscillatory condition would be relatively uniform within the skull, the location of the point or points of cavitation would be dependent on localized reduction of pressure because of the flow of fluid and the location of gas nuclei.

High-energy resonance in an elastic shell first requires structural continuity of the shell itself. Just as a crack in a bell destroys its properties of resonance, a fracture of the skull tends to prevent resonance cavitation. This is in accord with the literature reporting that in many cases in which the skull is fractured, the symptoms of concussion are less profound.

The second requisite for high-energy resonance in an elastic shell has to do with the means of exciting the resonance. The ringing of a bell requires a sharp blow from a relatively hard object. If the rate of rise of the exciting force is not sufficiently steep, high-energy resonance will not occur. In the experiments to date it has been found that it is most difficult to produce resonance cavitation directly from a sharp external blow, but resonance cavitation is most easily produced from the collapse of a contrecoup cavity (Fig. 14). The fact that the internal impact caused by the collapsing cavities drives the shell directly into the expanding phase of the oscillation is probably of significance. More significant, however, is the extreme sharpness of the impact caused by the collapsing cavities.

METHODS OF PRODUCTION OF CAVITATION

The three types of cavitation that we have considered so far are:

1. Coup cavitation

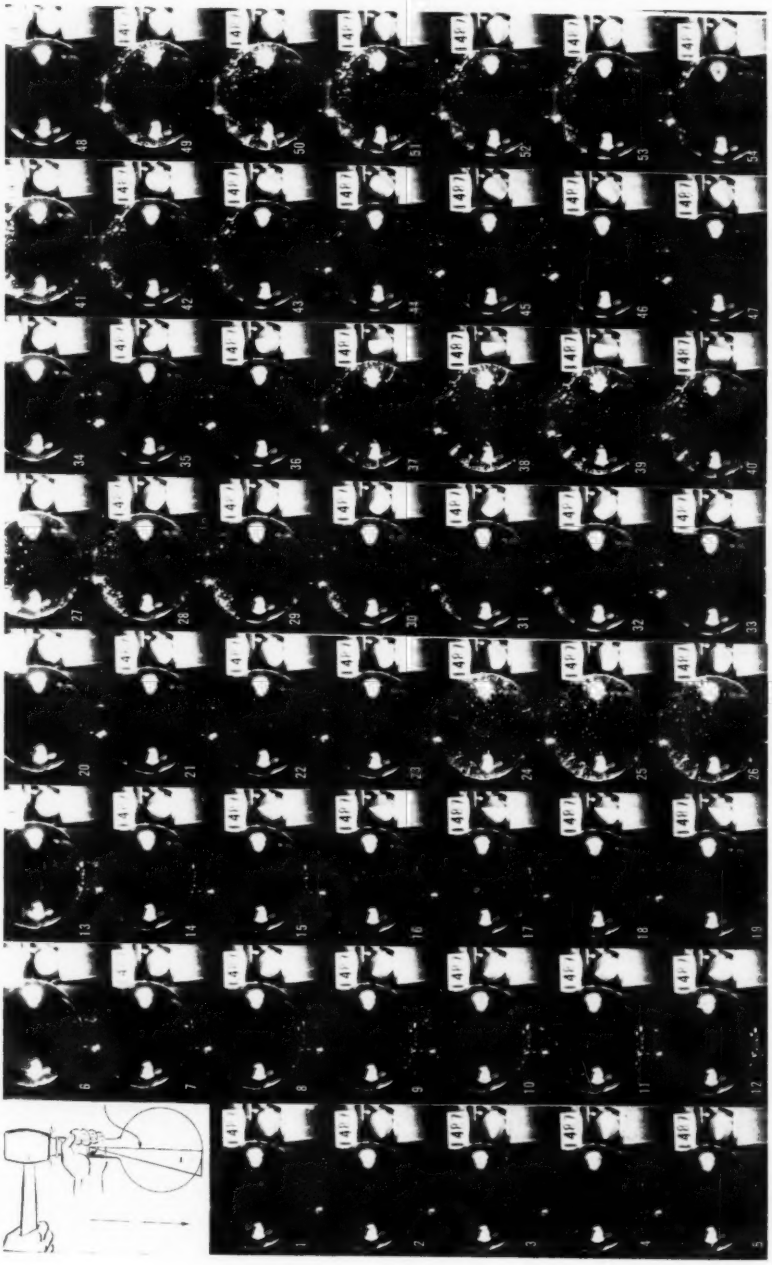


FIG. 12. High-speed photographs (4,000 frames per second) of a 2,000 ml. spherical glass flask being impacted from the top with a rubber mallet. The flask is filled with water half way up its neck. The stopper used was grooved along the sides to vent the interior of the flask. These photographs show the formation of the initial contrecoup cavities (frame 7) with subsequent cycles of resonance cavitation (frames 24, 37 and 49).

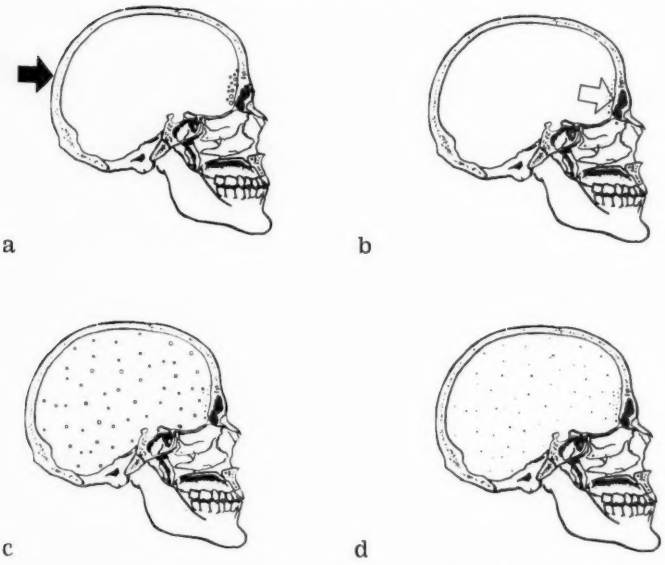


FIG. 13. Mechanism of brain injury caused by a blow to the back of the head. (a) Head is accelerated forward causing tension failure of the fluid at the front of the brain. (b) Upon cessation of acceleration of the head, the cavities at the front of the skull collapse with great violence, driving the skull into an expanding phase. (c) The expansion of the skull drops the internal pressure until cavitation occurs throughout the mass of brain. (d) As the skull then contracts, the cavities formed collapse with great violence, causing disperse damage throughout the brain. It is possible for several cycles of resonance cavitation to occur for a single impact.

2. Contrecoup cavitation
3. Resonance cavitation

In the experiments with the 2,000 ml. water-filled flask, one or more of the above types of cavitation were excited by the following methods:

1. Direct impact.
2. The glancing of a 22 bullet from the surface of the flask.
3. Impact of a loose-fitting wooden dowel floating in the neck of the flask.
4. A shock wave propagated in water with only the neck of the flask submerged into the shock medium.
5. A shock wave propagated in water with the unstoppered flask completely immersed in water.

EXPLANATION OF CHARACTERISTIC CONTUSIONS

The satellite petechial hemorrhages surrounding a focal hemorrhage may be explained on the basis of this theory in the following manner. As a cluster of cavities starts to collapse, the impacting force of those cavities collapsing initially is somewhat absorbed by the proximity of the adjacent cavities. As

the last cavity collapses, however, the cushioning effect of the adjacent cavities is no longer there and the full intensity of collapse caused by the inertia of the fluid is developed, resulting in the focal hemorrhage surrounded by the smaller satellite hemorrhages.

The characteristic conical contusion can be explained by the formation and collapse of a large hemispherical cavity against the rigid skull.

PUNCH-DRUNK SYNDROME

The well-known "punch-drunk" effect suffered frequently by boxers who have taken too many hard blows to the head indicates that the damage to the brain from these successive blows is cumulative in nature. The sectioned brain of a punch-drunk fighter shows small areas of damage dispersed throughout the brain. Such progressive damage may well be caused by minute cavities produced by sub-concussive blows.

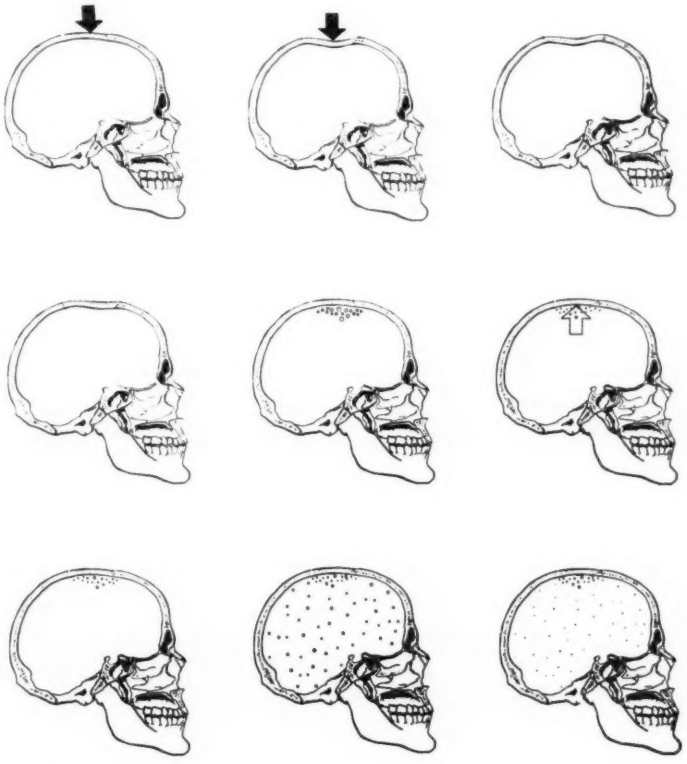


FIG. 14. The above sequence shows the occurrence of coup cavitation caused by snap-back of the locally deformed skull followed by resonance cavitation. Contrecoup cavitation can also occur simultaneously with the above coup cavitation because of the downward acceleration of the head.

ANIMAL EXPERIMENTATION

From the literature on animal experimentation, various researchers have reported difficulty in producing brain concussion in animals by impact to the head. Furthermore, the pathological findings in the experimental animals fail to show many of the characteristic types of damage found in the brain of man.

The above scale-effect findings are in accord with the theory being advanced. In the smaller animal, the length of fluid column along the impacting axis is much shorter than in man. The acceleration of the head required to produce contrecoup cavitation is, therefore, much greater.

ELECTRODYNAMIC CONSIDERATIONS*

The theories advanced to this point, attempting to explain the mechanism of brain concussion, have been based on the potential traumatic effect of the collapsing of cavities within the central portion of the brain.

Two basic objections to the above theory could be raised at this point. They are as follows:

1. Although the mechanism of the violent collapse of cavities within the centrum of the brain provides a plausible explanation of the origin of contusions of a focal nature, this mechanism fails to provide a sufficiently clear picture of just how functional centers are temporarily paralyzed because of the collapse of the cavities.

2. Collapse of the cavities within the centrum of the brain connotes structural cerebral injury, whereas pure brain concussion, as defined, is without structural alteration.

To attempt to fill the above apparent void in the theory presented, an additional supplemental mechanism is to be added to the mechanisms of cavitation already described.

There is a phenomenon, well-known in the field of cavitation research, known as "sonoluminescence." The name is derived from the fact that when certain fluids are driven to cavitation by ultrasonic generators, they will glow in the dark. The presence of this luminescence has been ascribed to high potential electrical fields being generated by the cavitation. An extensive bibliography on the subject of sonoluminescence may be found in the writings of Bergmann.[1]

If we truly have high potential electrical discharge associated with cavitation within the brain, we then approach a mechanism capable of producing brain concussion without overt structural injury.

CONCLUSION

A theory has been advanced on the dynamics of brain concussion and brain injury. This theory is based on the following mechanisms:

* Initial disclosure of this concept was made at the Office of Naval Research in Washington, D. C. on February 15, 1954.

1. Cavities are dynamically formed within the brain, producing contusions of a focal nature upon their collapse.

2. It is the violent collapse of the cavities that produces the tissue damage rather than the effect of the negative pressure.

3. Coup cavitation occurs at the site of the impact because of the snapback of the locally deformed skull.

4. Contrecoup cavitation, associated with acceleration of the head, occurs at a point opposite the blow because of negative pressures being developed that are greater than the tensile strength of the fluid.

5. Resonance cavitation, disperse in nature, is developed within the brain as a result of radial oscillation of the skull induced by the collapse of coup or contrecoup cavities or the passage of a sharp pressure wave.

6. The transient paralytic symptoms associated with concussion of the brain can be caused by two possible mechanisms:

a. The traumatic effect of minute cavities collapsing within or adjacent to the conscious centers.

b. The paralytic effect of an electrical discharge associated with cavitation occurring anywhere within the cranium.

If it can be established that concussion of the brain is produced by, or occurs simultaneously with, cavitation, it then may be possible to obtain considerable information on the threshold of concussion from research on impact on human cadavers.

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CASE REPORTS AND TECHNICAL NOTES

CEREBRAL GRANULOMA CAUSED BY *CRYPTOCOCCUS NEOFORMANS*

REPORT OF A CASE

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(Received for publication June 7, 1957)

In recent years the reported incidence of cryptococcosis has risen sharply. Slightly more than 300 cases of this disease are now on record.[7,13] Littman and Zimmerman[13] stated that there were 151 fatal cases reported by the National Office of Vital Statistics in a recent 4-year period. Although cryptococcosis has been reported from many countries around the world, the largest number of cases have occurred in Australia and the United States, particularly the latter.[7]

Since the central nervous system is involved sooner or later in the majority of the cases, neurologists and neurosurgeons are apt to be confronted with the diagnostic and therapeutic problems of this disease.[3] Not infrequently the history and neurological findings closely resemble the clinical picture of brain tumor because of the association of headaches, papilledema and progressive cerebral involvement. Yet in a thorough review of the literature, we were able to find but 18 examples of intracranial tumor caused by *Cryptococcus neoformans* (Table 1). Only those cases verified surgically or at autopsy were considered. Instances of minute, miliary lesions of the brain, of which there were numerous cases, were excluded for the purpose of this report.

Because of the rare occurrence of cyptococcosis in the form of cerebral granuloma of surgical importance, the following case is reported.

TABLE 1

Cases of intracerebral granuloma caused by cryptococcosis

No.	Year	Authors
1	1907	LeCount & Myers[12]
2	1929	Gáspár[9]
3	1930	Freeman[8]
4	1936	Mook & Moore[19]
5	1939	Longmire & Goodwin[15]
6	1942	Dickmann *et al.*[6]
7–8	1944	Swanson & Smith[20] (Cases 1 and 2)
9	1946	Krainer *et al.*[11]
10–13	1946	Cox & Tolhurst[4] (Cases 4, 6, 10 and 12)
14	1947	Hassin[10]
15	1949	Daniel *et al.*[5]
16	1952	Balakrishna Rao & Lilauwala[1]
17	1953	Liu[14]
18	1955	Manganiello & Nichols[17]

CASE REPORT

Summary. White female, aged 25, with progressive pulmonary infection caused by coexisting tuberculosis and cryptococcosis. Later development of meningitis and tumor of clavicle, both caused by *Cryptococcus neoformans*. Signs of right frontal lobe lesion. Pneumoencephalography. Arteriography. Surgical removal of granuloma from right frontal lobe. Temporary improvement neurologically. Convulsions. Expired 13 months after operation.

History. The patient, a 25-year-old divorced, American waitress, was admitted to the Santa Clara County Hospital on Nov. 5, 1952. A productive cough had been present for 5 years. Night sweats had been noted for 2 months, together with fatigue, loss of weight, and occasional episodes of chills and fever. A roentgenogram of the chest taken 9 months prior to admission was reported as negative. Another roentgenogram shortly before admission revealed extensive bilateral inflammatory disease with multiple cavities in the right upper lobe. There was a minimal pleural effusion on the left. Close contact with two individuals with active tuberculosis in the previous 5 years was admitted. Two years before admission, a spontaneous abortion occurred at 4 months.

Examination. She was tall, thin and sallow in appearance, with frequent cough. Her blood pressure was 94/58, pulse rate 100, and temperature 99°F. There was slight dullness over both apices on percussion. Breath sounds were distant but no rales were heard. The axillary lymph nodes were slightly enlarged. Neurological findings were normal with the exception of the left ankle jerk, which was slightly increased.

Laboratory Data. The blood count, urinalysis and serology were normal. The tuberculin skin test was positive in a dilution of 1:10,000 (OT). The coccidioidin skin test was negative in a dilution of 1:1,000. The sputum was positive for acid-fast bacilli on direct smear and by culture in November 1952.

Hospital Course. Therapy was started with streptomycin, paraaminosalicylic acid and pneumoperitoneum. In June 1953 chest films showed improvement in the right apical disease but also revealed a new lesion in the right lower lobe. A painful swelling developed in the right sternoclavicular region. Bloody fluid aspirated from this mass on July 8 was negative for tubercle bacilli. Headache, nausea and vomiting occurred during the next 2 days. Roentgenograms of the skull were normal. Spinal fluid pressure on July 10 was 200 mm. of water. The spinal fluid contained 57 white blood cells per c./mm. (lymphocytes 92 per cent, polymorphonuclear cells 8 per cent); total protein was 27 mg. per cent, and total sugar 54 mg. per cent. Acid-fast stains were negative for tubercle bacilli. Analysis of the spinal fluid on July 17 revealed a decrease in number of white cells to 23 per c.mm., an increase in total protein to 70 mg. per cent, but the total sugar content was unchanged.

The clinical impression was probable tuberculous meningitis. Headaches, nausea and vomiting persisted. Hemiparesis developed on her left side, beginning in the face.

On July 23, aspiration of the clavicular tumor yielded yeast-like organisms identified tentatively as *Cryptococcus neoformans* and later confirmed by cultures. There was weakness of the left arm, leg and lower face. The left leg was slightly spastic; the left arm and hand were flaccid. Meningitis caused by *Cryptococcus neoformans* was entertained as a likely possibility.

On July 24, spinal fluid analysis revealed 44 white blood cells per c.mm. Although no yeast organisms were found on microscopy, the culture was positive for *Cryptococcus neoformans* on August 13.

Pneumoencephalography was performed July 27. There was poor filling of the right lateral ventricle, particularly of the frontal horn, but without displacement. A right cerebral arteriogram was done immediately afterward. While this revealed no displacement of the anterior or middle cerebral vessels, a faint tumor shadow was noted in the right midfrontal region.

Clinical Diagnosis. The preoperative diagnosis was tumor of the right frontal lobe, possibly caused by *Cryptococcus neoformans*.

Operation. On July 27, 1953, immediately following arteriography, a right frontal bone

flap was turned down. A circumscribed nodule, 1 cm. in diameter, was found in the center of the surgical field, attached to the arachnoid but involving the cerebral cortex as well. The main mass of tumor was probed at a depth of 3 cm. in the mid-portion of the right frontal lobe. It was approached by removing a circular cap of cortex in the prefrontal region. The tumor was very hard, granular, nodular and sharply demarcated from the surrounding white matter.

Pathological Report. The tumor was 5×4×4 cm. in size (Fig. 1). The external surface was glistening, pale, yellowish-pink and somewhat bosselated. The cut surface was glistening, and mucoid in appearance. The central portion of the mass was a distinct yellow, while the outer narrow rim was gray-pink. India-ink preparations made from scrapings of the freshly cut surface revealed typical encapsulated yeast organisms, consistent with *Cryptococcus neoformans*, irregularly distributed between bands of hyalinizing fibrous connective tissue.

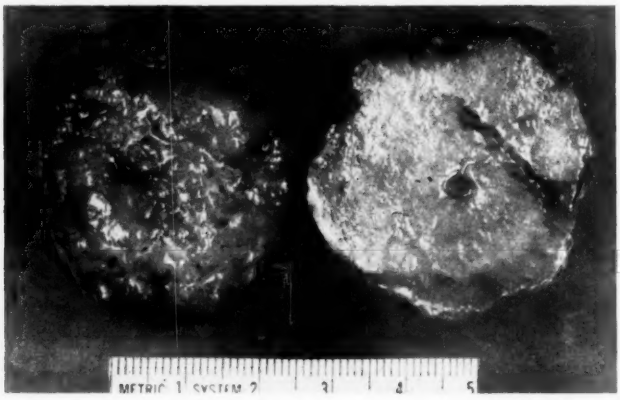

FIG. 1. Cross section of tumor removed from the right frontal lobe. Cut surface shown on the right.

Schiff's periodic acid stains were positive, as were cultures from the tumor. Sections of cerebral cortex revealed a granulomatous meningitis.

Subsequent Course. She had a complete flaccid hemiplegia on the left but was relieved of headache. On August 6, the medial half of the right clavicle was resected by Dr. Nels Ahnlund, consultant in orthopedic surgery. The mass over the clavicle measured 8×5 cm., was dark red in color, firm to palpation and contained a great deal of gelatinous mucoid material.

On August 31, *Cryptococcus neoformans* was cultured from the sputum. Motor function had returned to approximately 50 per cent of normal in the left leg, but the arm remained completely paralyzed.

Actidione therapy was started Sept. 1, 1953. Initial doses of 20 mg. intramuscularly once daily were given. However, dosages larger than 5 mg. were not tolerated because of vomiting, and this medication was discontinued after 1 week. Spinal fluid on September 9 contained 1 white blood cell per c.mm.; total protein was 52 mg. per cent. On September 4 the guinea pig that was inoculated with spinal fluid on July 13 was sacrificed. No acid-fast bacilli were found but there were numerous organisms identified as *Cryptococcus neoformans* in the mesenteric lymph nodes.

During October and November, 1953 there was little change in her condition. In December, 1953 she had a severe generalized seizure. She became drowsy and depressed, with loss of appetite. Her headaches returned.

On May 10, 1954, the spinal fluid was xanthochromic with a total protein of 600 mg. per cent; total sugar was 12 mg. per cent; there were 54 white cells per c.mm., and culture was negative for *Cryptococcus neoformans*.

In August 1954 she was no longer able to take nourishment by mouth. Frequent convul-

sions developed, predominating on the right side. She expired suddenly on August 14, 1954.

Autopsy. Gross findings. There was patchy consolidation of both lungs. The cut surface of the lungs presented a somewhat spongy, cystic appearance in all lobes. Some of these cavities were filled with a yellowish-gray caseous material. The brain weighed 1,250 gm. There was a large, healed surgical defect 5×5 cm. in diameter. There was extensive necrosis of the cerebral peduncles and mesencephalon. The ventricles were small and the right lateral ventricle was partially obliterated by fibrous adhesions. The surgical defect extended into the internal capsule. The cortex and meninges revealed only minimal thickening. The spinal cord was not remarkable.

Microscopic Examination. Some of the spaces in the lung were lined by caseating granulomatous inflammatory tissue with many multinucleated Langhan's cells. Schiff's periodic acid stain failed to reveal the presence of fungi. An acid-fast stain was also negative. Elsewhere there were extensive residuals of chronic inflammation with edema and patchy confluent bronchopneumonia. A few of many sections of the central nervous system stained with Schiff's periodic acid technique showed only an occasional organism consistent with *Cryptococcus neoformans.*

Comment. The onset of symptoms in this case was typical of pulmonary tuberculosis. When signs of meningeal complications appeared, these were attributed to tuberculous meningitis. When *Cryptococcus neoformans* was isolated from the clavicular mass, the possibility that the entire clinical picture was caused by cryptococcosis seemed very likely.

When the signs of a focal cerebral lesion appeared, the diagnosis of cerebral granuloma caused by *Cryptococcus neoformans* was made presumptively because the organisms had been identified in smears from the clavicular mass. The postoperative survival period was far longer than predicted in view of the advanced degree of both diseases (tuberculosis and cyptococcosis). The association of pulmonary tuberculosis with systemic cryptococcosis has been reported but rarely.[16,21] This unusual feature will be discussed separately in a subsequent report.[18]

DISCUSSION

In further study of the 18 cases reported in Table 1, it was observed that although various operative procedures were performed in many instances, there were only 11 cases in which granulomas of the brain caused by *Cryptococcus neoformans* were actually removed surgically (Table 2).

The case reported by Gáspár in 1929[9] was that of a 52-year-old blacksmith who had headaches and pain in the neck for 2 months. Vertical nystagmus, nuchal

TABLE 2

Surgical removal of cerebral granulomas caused by cryptococcosis

No.	Year	Author	Location	Size of Granuloma
1	1929	Gáspár[9]	L. frontal	6 cm.
2	1930	Freeman[8]	R. cerebellum	3 mm.
3	1936	Mook & Moore[19]	R. frontal	"pea size"
4	1942	Dickmann *et al.*[6]	L. cerebellum	6 cm.
5	1944	Swanson & Smith[20]	R. cerebellum	4×5 cm. (Case 2)
6	1946	Krainer *et al.*[11]	L. frontal	"size of tennis ball"
7	1949	Daniel *et al.*[5]	L. cerebellum	4.5×3.5 cm.
8	1952	Balakrishna Rao & Lilauwala[1]	R. parietal	1.2×1.2 cm.
9	1952	Beeson[2]	R. temporal	miliary lesion
10	1953	Liu[14]	R. frontal	miliary lesion "size of mothballs"
11	1955	Manganiello & Nichols[17]	R. ventricle	6×5×4 cm.

tenderness, unsteadiness of gait, pleocytosis and papilledema were the chief findings. After an unsuccessful attempt at ventriculography, a subtemporal decompression was done. Temporary improvement was interrupted by severe jacksonian seizures 3 months later. A tumor 6 cm. in size was removed from the "motor area on the left." Although the postoperative hemiplegia improved considerably, the patient then deteriorated and died a few weeks later. *Cryptococcus neoformans* was demonstrated in the surgical specimen as well as in the brain at autopsy. This was the first reported case of surgical removal of this type of granuloma from the brain.

Dickmann *et al.*[6] in 1942 reported a case in which a large cerebellar tumor caused by *Cryptococcus neoformans* was removed. The patient progressed remarkably well postoperatively but left the hospital 1 month later against advice. At that time there was no evidence of activity of the disease elsewhere but contact with the patient was lost.

Swanson and Smith[20] in 1944 reported 2 cases of cerebellar tumor caused by *Cryptococcus neoformans*. In their first case, surgery was not performed because the patient expired suddenly while in the hospital undergoing diagnostic study. In their second case the pre-operative diagnosis was cerebellar tumor probably caused by *Cryptococcus neoformans*. The patient, aged 36, had been rejected from the Army 2 years earlier with a pulmonary lesion regarded as tuberculous. However, *Cryptococcus neoformans* was isolated from the sputum and gastric contents. Because of headaches, pain in the neck, vomiting, ataxia, papilledema and a right abducens paresis, ventriculography was done. The tumor measured 3×3 cm. and involved the right cerebellar tonsil. After 4 months of marked improvement, there were signs of recurrence. At the second operation the mass measured 4×5 cm. Five days later the patient lapsed into coma and expired.

Krainer *et al.*[11] in 1946 described the case of a Sikh, aged 32 years, who had a draining supraorbital mass, a swelling in the right hip and a pulmonary lesion. *Cryptococcus neoformans* was isolated from the mass over the hip. Orbital exploration revealed the inflammatory mass extended to the dura mater. Three months later, after a convulsive seizure, signs of increased intracranial pressure and a left frontal lobe lesion appeared. At craniotomy, a mass, "the size of a tennis ball," was removed. An excellent recovery was made. At the last follow-up examination, 11 months later, the only residual finding was increased reflexes in the right leg.

Daniel *et al.*[5] in 1949 described the case of a miner, aged 50 (Case 2), who had a clinical history of 2 years, beginning with consumptive symptoms, later complicated by the features of subacute meningitis. Although the radiographic appearance of the lung fields was said to be typical of tuberculosis, tubercle bacilli were never found in samples of the sputum. Neurological findings indicated a left cerebellar lesion. At operation, a gelatinous mass measuring 4×3×3 cm. was removed from the left cerebellar hemisphere. After a brief period of considerable improvement, his condition deteriorated and he expired 6 months after operation. No autopsy was performed.

Balakrishna Rao and Lilauwala[1] in 1952 reported removal of a cerebral granuloma caused by *Cryptococcus neoformans*. Convulsions were the patient's only symptom. Pneumoencephalography revealed a mass in the right parietal region. The patient was apparently cured at the time their paper was published.

Liu[14] in 1953 reported the case of a man, aged 35, who collapsed at work and had several seizures. Examination when he recovered from this episode revealed increased patellar reflex on the left, positive Babinski sign on the left, and absent

abdominal reflex on the left. Roentgenograms of the skull revealed a cluster of 5 small calcifications resembling mothballs in the right frontal region. Air studies revealed slight blunting of the right frontal horn. The lesions were excised. An excellent postoperative course followed. One year later he was asymptomatic and no abnormal findings were noted on examination.

In the case described by Manganiello and Nichols[17] in 1955 the tumor was found in the right lateral ventricle. The patient, a 61-year-old male, had a 2-week history of headaches, blurring of vision and one "blackout spell." There were clinical signs of a right hemispheral lesion without papilledema. While undergoing studies to determine the exact cause of the pleocytosis found at spinal tap, the patient's condition became much worse. Ventriculography demonstrated a mass obliterating the right lateral ventricle. This measured 4×5×6 cm. when removed at operation and was attached to the choroid plexus. A downhill course followed and the patient died 10 days later.

In spite of the rather large size of the lesions, papilledema was present in but 4 of the 11 cases summarized. Of this group of 11 patients, all but 3 died within a few weeks following operation. One patient (Daniel *et al.*[5]) left the hospital against advice 1 month postoperatively. Only 2 patients were alive and apparently well for as long as 1 year after surgery (cases of Krainer *et al.*[11] and Liu[14]). In spite of this long period of apparent recovery, the prognosis in such cases must remain guarded because this disease may become indolent for many years and ultimately be fatal. The case reported by Beeson,[2] followed for 16 years, is a remarkable example of this aspect of cryptococcosis.

It is the opinion of the authors that when a patient with suspected or proven cryptococcosis shows signs of a localized intracranial lesion, with or without increased intracranial pressure, cerebral contrast studies should be undertaken and the tumor, if found, be removed; for in spite of the generally poor prognosis of such cases, surgical treatment can be rendered with relief of distressing symptoms and in some instances apparent cure, although it is doubtful that permanent cures can be obtained with present methods.

SUMMARY

A case of large cerebral granuloma caused by *Cryptococcus neoformans*, treated surgically with 13 months' survival, is reported. Review of the literature revealed only 8 similar cases. The lesion measured 5×4×4 cm. in size, was located in the right frontal lobe and was associated with cryptococcosis of meninges, bone and lungs, and pulmonary tuberculosis.

The authors wish to express their appreciation to Dr. Walter Freeman for his kind suggestions in the preparation of this manuscript.

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TERATOMA OF THE CONUS MEDULLARIS

REPORT OF A CASE

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(Received for publication June 18, 1957)

Teratomas of the conus medullaris apparently are rare. In a search of the literature only 3 cases were found in which the tumor was located in the vicinity of the conus medullaris. The following is a report of such a case encountered at the Kaiser Foundation Hospital in Los Angeles.

CASE REPORT

Hospital No. W.349252. N.S., a female aged 44 years, was admitted to the hospital on Jan. 27, 1957, because of weakness in both legs for 3 years and loss of control of the urinary bladder and rectal sphincter for 2 years. Four years prior to admission, she had an excruciating pain radiating along the lateral side of the right lower limb down to the external malleolus. Resting in bed aggravated the pain and walking eased it. Meanwhile, the patient felt weak at both ankles, the right more than the left. The pain gradually disappeared 1 year later. Nevertheless, the weakness in both legs progressed slowly and she could hardly stand on her toes. She lost the control of her bladder. In association with orgasm during sexual intercourse, she involuntarily emptied her bladder. As time went on, she also was unable to control her anal sphincter.

Neurological Examination. There was a mild degree of scoliosis of the lumbosacral spine. Tenderness was elicited over the spinous process of D10 to D12. Her gait was limp. There was marked weakness in plantar flexion of both feet. The right was weaker than the left. There was a distinct sensory level of hypesthesia at D12 on both sides. A saddle pattern of marked hypesthesia was elicited below the level of L2 with anesthesia along the distribution of S1 on both sides. There was also impairment of temperature sensation in this area. Nevertheless, both the vibration and position sense of the lower limbs were intact. Rectal examination showed that the anal sphincters were atonic. Both knee jerks were depressed but present and equal. Both ankle jerks were absent.

Laboratory Findings. Roentgenogram of the dorsal spine showed a slight widening of the interpedicular space at D12.

Lumbar puncture revealed an initial pressure of 170 mm. of water. The cerebrospinal fluid was clear, containing 3 mononuclear cells per c.mm., and 121 mg. per cent of total protein. The manometric test showed a complete block. Myelogram disclosed a "cap-pattern" of a complete block at the level of D12.

A preoperative diagnosis of an intradural and extramedullary tumor was made.

Operation. On Jan. 30, 1957, a complete laminectomy was performed with the removal of the laminal arch of D12, L1 and partial L2. There was no pathology seen outside the dural sac. Palpation through the dura mater revealed an indurated mass at the junction of D12 and L1. A tumor, the size and shape of an olive, was found intradurally in the left ventrolateral aspect of the conus medullaris, with its upper pole pushed into the conus. It wore the conus as a cap. The roots of the cauda equina were wrapped around the tumor and were crowded to the right. There were several large and tortuous blood vessels on the dorsal aspect of the conus, as well as along some of the roots of the cauda equina. The tumor was pale in color and firm in consistency. It was cystic and encapsulated. There were three small cysts

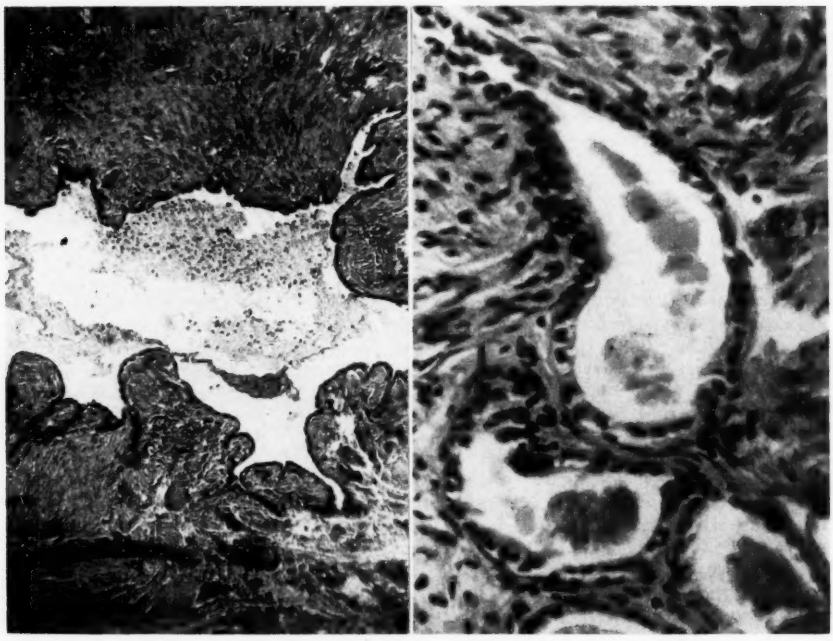

FIG. 1 (*left*). Low power view showing cystic area of the tumor. (×30)
FIG. 2 (*right*). Showing acini containing colloid. (×240)

in the rostral portion and four in the lower part of the tumor. The total content of these cysts was about 2 cc. The cystic fluid was xanthochromic in color. The cysts were evacuated and the tumor was completely removed, en masse, after it had been freed from the conus medullaris. The roots of the cauda equina and the conus were well preserved.

Postoperative course was uneventful. On the 6th postoperative day the patient could stand well on her toes and the weakness in the legs had practically disappeared. Two days later, she partially regained the control of her bladder and anal sphincters. Since the operation, she had been complaining of an annoying tingling sensation and frequent cramps in both legs. These subsided on the 9th postoperative day. Examination on this day still demonstrated the saddle pattern of hypesthesia, and an absence of ankle jerk on both sides. She was discharged on the 10th postoperative day.

The patient was seen again $5\frac{1}{2}$ months later. There was only partial recovery of bladder function as indicated by the cystometric test. There was no weakness noticeable in the legs. Hypesthesia of the sacral distribution was minimal.

Pathologic Studies. Gross description. The surgical specimen was an encapsulated, ovoid-shaped lesion, 2 cm. in its greatest dimension. On cut section, the tumor was seen to be mostly solid, but it did contain several small, cystic areas. The largest cyst measured up to 4 mm. in diameter. The tumor was whitish-gray with sparse yellowish areas, and had a fibrous consistency.

Microscopic description. The tumor was composed of multiple kinds of tissue that are foreign to this area. Most of the solid areas consisted of nonstriated muscle which, in some places, formed the wall of the cavities. The cavities were lined by flattened columnar epithelium which was not ciliated (Fig. 1). Several small bundles of peripheral nerves were seen

running through the tumor, and adult fat tissue was interspersed between some of the bundles of nonstriated muscle. In a few areas, there were structures having the appearance of thyroid acini with colloid in their lumina (Fig. 2).

Diagnosis. We believe that this represents a teratoma because of the presence of various types of tissue, glandular, nerve fibers, muscle, fat and fibrous elements.

DISCUSSION

This case presents a typical clinical history and findings of a lesion involving the conus medullaris and the roots of the cauda equina. The radicular pain experienced by the patient in the right leg during the early course of her illness was probably a result of pressure exerted upon the corresponding nerve by the tumor against the right side of the spinal canal. Later, as the tumor grew and the pressure increased, the pain was replaced by anesthesia in the area involved. At operation, the tumor was seen to be located in the left ventrolateral portion of the spinal canal. The roots of the cauda equina as well as the conus medullaris were displaced and crowded to the right by the tumor. This probably explains the fact that the right leg was involved more than the left.

Including the present case, only 4 teratomas of the conus medullaris have been recorded in the literature.[1,2,3] In 2 of these cases, including ours, the tumor was completely extirpated.[1]

SUMMARY

A case of teratoma of the conus medullaris with complete removal and recovery of the patient is described.

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THE TREATMENT OF TORULA MENINGO-ENCEPHALITIS WITH AMPHOTERICIN B*

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(Received for publication August 2, 1957)

The eventual course of meningo-encephalitis caused by *Cryptococcus neoformans* is well known. Any agent that improves or arrests the course of this illness should be brought early to the attention of those physicians who see and diagnose this infection. Cryptococcosis, torulosis, and European blastomycosis refer to the same mycotic disease caused by the *Cryptococcus neoformans*. This fungus is widespread in nature and reports of the disease it produces have come from nearly all areas of the world. The greatest number of cases have been reported from the United States and Australia. This infection, which fails to cause a very great tissue response, is considered to be air-borne, with the reservoir being in the soil. Although the infection is air-borne, it is disseminated from the lungs through the blood stream. The central nervous system is particularly susceptible and this involvement is usually manifest as a meningo-encephalitis. Once there is involvement of the central nervous system, a fatal outcome is almost certain.[2]

Historically the first record of the identification of this organism, which has now come to be classed as *Cryptococcus neoformans* but is also known as *Cryptococcus hominis* and *Torula histolytica* was first isolated and described in 1894 by Busse. Sanfelice at the same time isolated a yeast from peaches, to which he gave the species term of neoformans. The first human case of torulosis of the nervous system properly diagnosed was reported by Versé in 1914. Two years later, Stoddard and Cutler reported 2 cases naming the organism *Torula histolytica* because of what they thought to be a histolytic action of the organism in producing cysts in the tissue. Apparently, there are many strains of pathogenic cryptococci, possibly twenty-two in all, of varying pathogenicity but biologically similar.

Although considered a rare disease, torulosis is the most frequent cause of mycotic meningitis in man. There is an increasing importance of mycotic disease in the United States; the total deaths attributed to this group was greater in each year from 1949 through 1952 than the combined fatalities caused by Rickettsia, protozoal and helminthic diseases. Notwithstanding this increase in incidence, it is believed that many cases go unrecognized. Many cryptococcal infections are diagnosed only post mortem and based on the small percentage of cases in which autopsy is performed, the actual incidence of cryptococcosis must be much higher than that conveyed by the medical literature.[2]

Clinically, cryptococcosis of the central nervous system may manifest itself in a variety of ways. Some of the diagnoses that have been made, and patients treated for, were: spinal cord tumor, brain abscess, general paresis, brain tumor, encephalitis and more particularly tuberculous meningo-encephalitis. In the case reported here

* Appreciation is expressed to Gavin Hildick-Smith, Associate Medical Director of The Squibb Institute for supplying the Amphotericin B.

the patient had previously, on two hospital admissions, been worked-up and treated as having a brain tumor. In a review of the literature by Carton and Mount[1] in 1951, it was revealed that there were 42 cases in which neurosurgical procedures were performed, with a total of 62 operations. There were 24 exploratory operations: 12 supratentorial, 9 infratentorial, and 3 laminectomies. In addition to this there were 11 decompressive procedures. Localized cryptococcal granulomata may occur and become of sufficient size that they require attention as a mass lesion. The diffuse cryptococcal leptomeningitis may also produce a picture of an expanding, intracranial lesion. In the report cited[1] there was no mention of a case in which there had been an obstruction of the aquaeductus Sylvius and a Torkildsen's procedure performed.

CASE REPORT

B.G.-001 408. A 46-year-old white male was admitted to the Eugene Talmadge Memorial Hospital on Nov. 1, 1956, at which time he was stuporous and had a left hemiplegia. In April 1954 he had been admitted to another hospital because of nausea and vomiting, visual and auditory hallucinations, unsteadiness on his feet, and nuchal rigidity. Diagnostic studies performed at that time included a pneumoencephalogram and it was thought he had a tumor of the right parietal lobe. Biopsies were taken which were reported to have shown evidence of a malignant brain tumor. The patient had a subtemporal decompression performed on the right and the family was advised he had a malignant tumor and that nothing more could be done. He apparently showed an improvement in his mental state for a matter of several months but began to have severe headaches, progressive weakness of the left lower extremity, nausea and vomiting, and a cloudy sensorium. It was noted by the family that the subtemporal decompression bulged. He was admitted to another hospital where the site of decompression was pulseless, tense and firm. He was responsive only to deep and painful stimuli. An exploratory trephine was placed in search of tumor. The following day he was transferred to our hospital.

Examination. Blood pressure was 160/100, respiratory rate 18, pulse rate 78, and temperature 36.8°C.

Scars of the previous trephinations in the frontal region were on each side of the sagittal suture and there was another old scar, 8 cm. long, perpendicular to the right zygomatic process. This was over the site of the bulging temporal decompression. There was a fresh wound and trephine opening over the right parietal area. The brain was tense, prominent and nonpulsile. Pupils were dilated but did react. There was nuchal rigidity with stiffness and pain on motion.

Roentgenograms of the skull revealed stippled calcification in the region of the dorsum sellae and erosion of the posterior clinoid processes. Right carotid arteriography revealed evidence of internal hydrocephalus. Ventriculography performed through the previously placed trephine revealed a complete block between the 3rd and 4th ventricles; 10 cc. of phenolsulfonphthalein instilled in the right lateral ventricle failed to be recovered in the lumbar subarachnoid space. With a ventricular needle in place, air was placed in the lumbar subarachnoid space and this ascended to fill the 4th ventricle and the great cistern, which did not seem to be displaced or of unusual configuration. It was felt that the patient had an internal hydrocephalus caused by aqueductal block.

Operation. A Torkildsen procedure was performed, with immediate improvement in the patient's sensorium.

The spinal fluid, examined by Dr. Shepherd of the Clinical Laboratory, Department of Pathology, Medical College of Georgia, revealed *Cryptococcus neoformans*, both encapsulated and non-encapsulated. The count of organisms was extremely heavy. Culture showed an extensive growth. Spinal fluid glucose was 73 mg. per cent; chlorides were 130 mEq.; colloidal gold curve read 5555442100; Pandy was reported as 4 plus, and there were 11 white blood cells, with 6 polymorphonuclear leucocytes and lymphocytes.

Course. The patient was immediately started on tetracycline, nystatin, Ethyl Vanillate, and sodium bicarbonate. In spite of this medication the patient continued to run a downhill course and appeared moribund. Repeated studies of the spinal fluid showed increasing counts of organisms and positive cultures. On Dec. 6, 1956, the patient was started on Amphotericin B, 50 mg. I.V. daily; 2 days later he began to show improvement. He received a total of 2 gm. of Amphotericin B over a period of 40 days at 50 mg. daily. The Amphotericin B was stopped on Jan. 18, 1957. A lumbar puncture on Jan. 19, 1957 revealed no evidence of *Cryptococcus neoformans*. The cultures were negative. The spinal fluid smears were negative. The patient was discharged on Jan. 22, 1957.

He was seen again as an out-patient on Feb. 13, 1957. The site of the decompression was flat and pulsile. The patient showed steady improvement in strength and was completely ambulatory, although he had tremors of both arms and an involuntary tremor. He had no headache, his sensorium was perfectly clear and he had been doing odd jobs about the home. He was admitted for 24 hours for a lumbar puncture. His opening pressure was 100 mm. of water with a negative Queckenstedt response. The fluid was slightly xanthochromic but clear. A smear of the spinal fluid showed no evidence of organisms, and cultures of the spinal fluid were negative. Urinalysis was normal. Nonprotein nitrogen was 38 mg. per cent. Fasting blood sugar was 102 mg. per cent. Hemoglobin was 16.4 gm. and hematocrit 46. Count of white blood cells was 8,250, with 50 per cent segmenters, 34 per cent lymphocytes, 10 per cent monocytes, 5 bands and 1 eosinophil. The platelets appeared normal. The red blood cells were normal. Prothrombin time was 100 per cent at 12.3 sec. Spinal fluid sugar was 68 mg. per cent, chloride 11 mg. per cent, protein 350 mg. per cent, Pandy 3 plus, and there were 32 cells/cc.

The patient was seen again on Feb. 27, 1957. His course had been one of progressive improvement. He continued to show a slight involuntary tremor of the extended extremity on the left. There had been improvement in the tremor in the right upper extremity. The gait showed slight incoordination, mainly in the left extremity. Reflexes were hyperactive on the left.

On March 27, 1957 his general condition was improved. He had gained 23 lbs. since his discharge. Neurological findings were essentially as seen on Feb. 27, 1957. There were still hyperactive reflexes and slight tremor on the left. The site of the right temporal craniotomy was flat and pulsile, and there was no evidence of any active disease. The patient had been maintained on Dilantin 100 mg. b.i.d. and Phenobarbital 100 mg. at bedtime. He was receiving no other medication.

He was seen again in April 1957. At this time he drove his automobile to the clinic. He had returned to doing his work on a small farm and he was asymptomatic. A lumbar puncture performed at this time showed no organisms and there was no evidence of growth on Sabouraud's culture after 10 weeks' incubation at 27°C.

Since this report was submitted for publication, the patient was seen again in June 1958. He continues to remain well and is carrying on his duties on a farm. The cerebrospinal fluid remains normal.

DISCUSSION

Amphotericin B, an antibiotic formed by a species of Streptomyces isolated from soil obtained from South America has been shown *in vitro*, and in animals *in vivo*, to inhibit the growth of *Cryptococcus neoformans*.

The chemical structure of Amphotericin B is not known. It is a relatively stable antibiotic, even at temperatures as high as 40°C. Absorption from the gastrointestinal tract appears to be minimal. By the intravenous route the bioactivity of the blood plasma is maintained high for several hours. The drug is quickly adsorbed to the red blood cells and the maximum excretion by the kidneys occurs during the first 3 hours. Amphotericin B appears to be antifungal not only against *Cryptococcus neoformans*, as shown *in vitro*, but also against other yeast and yeast-like

fungi, including *Candida albicans, Blastomyces dermatitidis, Blastomyces brasiliensis, Sporotrichum schenckii,* and *Histoplasma capsulatum.* Animal *in vivo* studies show it to be effective not only in *Cryptococcus neoformans,* but also in *Candida albicans, Coccidioides immitis, Histoplasma capsulatum* and *Trichophyton mentagrophytes.*

The mode of action of Amphotericin B is fungicidal and Mycostatin appears to have an additive or synergistic effect. Amphotericin B appears to have little or no antibacterial activity.

Administration. Amphotericin B is formulated as a freshly prepared sterile suspension and is administered by mixing 50 mg. in 250 cc. sterile 5 per cent glucose in water. Effort must be made to have all of the suspension agitated into solution before administration by slow intravenous drip over a period of approximately 5–6 hours. Mild febrile reactions may be observed during and after the administration. If a febrile reaction occurs during administration, therapy is halted until this reaction is over. Phlebitis at the site of injection may be seen, but usually this will not occur if the rate of injection is sufficiently slow. Frequent inspection of the dripping suspension should be made to avoid the administration of precipitated material; this can be prevented by repeated agitation.

This patient presented a very confusing problem. He had been originally operated upon and advised that he had a malignant glioma of the brain. He had shown a temporary improvement following the subtemporal decompression and biopsy in April 1954 only to have a recurrence of his headache, nuchal rigidity, and clouding of his sensorium. He was seen again in October 1956 because of a progressive downhill course at which time the skull was trephined and exploration with a needle was performed in an attempt to hit a tumor cyst or to localize a mass lesion. He then was admitted to our hospital for evaluation and treatment.

It was postulated that his left hemiplegia was the result of increased intracranial pressure secondary to the internal hydrocephalus, which forced the right motor strip tight against the bony edge of the decompression craniectomy of the right temporal and parietal bones, making this a paralysis secondary to presssure alone and not caused by a localized encephalitis. This hypothesis was borne out by the fact that the hemiparesis showed immediate improvement after decompression of the lateral ventricles with the Torkildsen procedure. Although this patient had received the various drugs mentioned, namely; mystatin, Ethyl Vanillate, tetracycline and alkalinization by excessive doses of sodium bicarbonate, his course continued downhill. The use of these other drugs could well serve as a control in this individual, inasmuch as the spinal fluid showed increased cell count and growth and the clinical condition of the patient worsened daily, until the addition of Amphotericin B, when he began to improve.

ADDENDUM

Since submitting this report, a second patient with Torula meningo-encephalitis has been treated with Amphotericin B. The cerebrospinal fluid became free of organisms during treatment and has remained so for 7 months. The patient is well clinically and has resumed his usual activities.

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ON CERVICAL CORDOTOMY—A NEW TECHNIQUE

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(Received for publication August 17, 1957)

Several factors determine the outcome of anterolateral cordotomy to relieve pain and produce satisfactory sensory loss. The result depends upon factors that have an (1) anatomical, (2) physical, and (3) mechanical basis.

Anatomical Factors. The experience of Voris,[10] of French and Peyton,[1] and our own experience[2] indicate wide variation in body representation of pain-conducting fibres in the lateral spinothalamic tract. Complete return of sensibility to pain and disappearance of a sensory level as long as 10 years[2] after successful cervical cordotomy suggest that other pathways of the spinal cord may become pain conductors or that regeneration of previously destroyed pain fibres may occur.

Anatomical texts[6,9] show the lateral spinothalamic tract as lying superficially in the anterolateral quadrant of the spinal cord. Clinical observations, however, of patients who have had cordotomy are inconsistent with these designated patterns. After an extensive cordotomy it is not unusual to find sensation of pain preserved in the sacral and lumbar dermatomes. In view of present concepts of the most superficial location of these fibres in the lateral spinothalamic tract, this persistence of sensation of pain is difficult to explain. It implies a widespread distribution of the pain-conducting fibres. Ipsilateral representation of the lateral spinothalamic tract in the anterolateral quadrant has been reported.[1,10] Voris[10] presents evidence that, at times, the sacral fibres may lie deep and medial to the anterior root and a great part, even in the posterior funiculus. This observation is important for, if some of the lowermost sacral fibres lie above the plane of the dentate ligament, cordotomy above this level is necessary to destroy the sacral representation. Kahn[5] stated that if high dorsal cordotomy beginning at the insertion of the dentate ligament is carried 4 or 5 mm. deep and 2 mm. anterior to the emergence of the anterior root, analgesic levels are produced which rarely fall. The experience of Roulhac[8] and others[7] with high cervical cordotomy suggests that representation of the upper trunk and limb is a compact bundle lying in a location more dorsal and superficial than at the lower levels in the cord. Because variations such as these are possible, it is evident that unilateral cordotomy, no matter how extensively performed, may not always be satisfactory. Common experience has shown, however, that the best results are obtained when incision of the anterolateral quadrant is made as complete as possible.

Physical Factors. Though one thinks of the spinal cord as a rigid cylinder, indeed it is not. As Hamby[3] pointed out, the physical factors involved in rotating the cord to allow ready access for the incision in cordotomy account for considerable distortion of the cord (Fig. 1A). This distortion prevents uniform section of the more anterior and medially placed fibres, unless an incision is made of greater than the desired depth. The pyramidal tract becomes elongated in the dorsoventral diameter and may be injured when the section is applied at the recommended right angle to the cord. Because we believe that this distortion by rotation contributes to the vari-

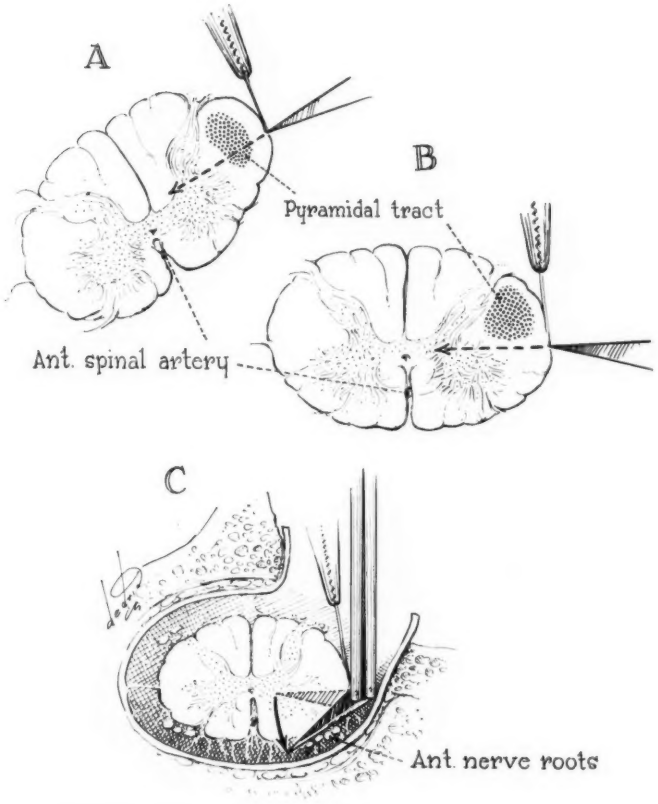

FIG. 1. (A) Theoretical distortion of 45° rotation of a semisolid cylinder (spinal cord)—adapted from Hamby.[3] (B) Proposed plane of penetration of blade of the knife into minimally rotated spinal cord. (C) Section of spinal cord produced mechanically.

able results and morbidity of cordotomy, we suggest that section be accomplished so that the normal position of the cord be disturbed as little as possible (Fig. 1B).

Mechanical Factors. From a mechanical standpoint, it is difficult to make a complete section of a quadrant of the cord when a cutting blade is applied at right angles to it because the fixed limits and contour of the spinal canal prevent manipulation of an instrument within the space. Under such conditions the section must be made with a constant anteriorly directed force. The thin dentate ligament which has been grasped for anchorage may be easily torn, disturbing the blade-cord relationships so that the blade may be withdrawn inadvertently before the entire quadrant has been cut (Fig. 1C). But, if the blade can be made to swing through an arc of 90°, a maximum, uniform section can be accomplished with a minimal disturbance of the position of the cord. We believe that a method of reducing distortion of the cord to a minimum and of making the incision consistently maximum in cordotomy, will give

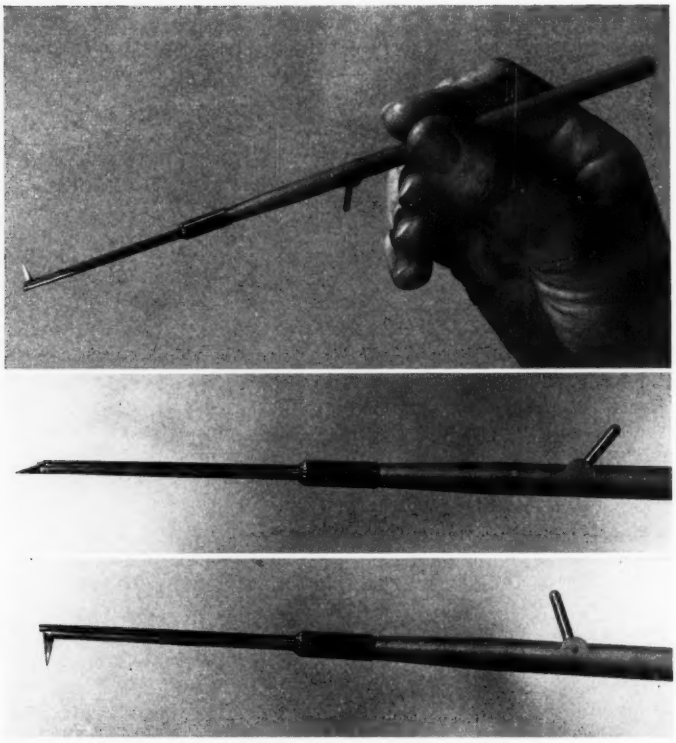

FIG. 2. Photograph of instrument before (above and below) and after (middle) blade has passed through an arc of 90°.

more uniformly successful results. This, we feel, has been achieved with an instrument* of new design.

THE INSTRUMENT

The instrument (Fig. 2) consists of a 7″-long stainless-steel barrel, 6 mm. in diameter, from one end of which pass two steel leaves. On the distal end of one of these leaves, a triangular blade, 8 mm. long, is secured. The side of the blade measures 2 mm. and the exposed cutting portion of the blade extends $6\frac{1}{4}$ mm. The exposed supporting structure for the blade measures 2 mm. on end. A toggle, placed approximately midway on the shaft of the instrument, actuates the second leaf to drive the blade through an arc of 90°. With the instrument held in one hand, much as one holds a pencil in writing position, the toggle is moved by a force of 2–3 ounces applied through the index finger. This degree of force prevents movement of the blade before proper placement, yet it allows smooth, uniform and controlled action while the blade is in motion. The mechanism is so designed that the degree of a proposed incision can be determined at any time by observing the angle through which the toggle has passed. The blade, which can be rotated through any angle suitable to the operator, is held securely by a ser-

* This instrument is obtainable from Hastings Laboratories, Bass River, Massachusetts.

rated sleeve at the distal end of the barrel shaft. Except for the blade and its pins for fixation, the entire instrument is made of stainless steel. It requires no lubrication and may be sterilized by autoclaving or by the cold method. The sharpness of the cutting blade is maintained by careful handling of the instrument and by a protective case for storage. The blade may be sharpened with a fine hand hone.

TECHNIQUE OF OPERATION

The operation is made with the patient in the sitting position, the dangers of postural hypotension and air embolism being guarded against as outlined by Hamby and Terry.[4] The neck is sharply flexed, prepared and draped. The skin and paraspinal muscles are infiltrated with 1 per cent solution of Xylocaine. A midline incision is then made from C3 to C6 spinous processes, and the muscles are reflected unilaterally. Excellent retraction is obtained with the Taylor spinal retractor, held in place by a stout rubber band fixed to the drape with an Allis clamp. The hemilamina of C4 vertebra (and C5 on the opposite side when bilateral cordotomy is to be done) is removed as far medially and laterally as possible, together with the ligamentum flavum above and below the lamina. Epidural veins are cauterized. The dura mater is then incised about 3 mm. from its most medial exposure and cut in somewhat circular fashion (the convexity of the flap facing medialward), with the incisions carried as far laterally as possible. A 1-cm. flap is adequate but the entire length of the exposure can be used if necessary. In opening the dura mater, one is careful not to open the arachnoid. The arachnoid is then nicked with the blade of a knife and torn superiorly and inferiorly, preventing the lateral edge of the cut from falling upon the cord, as this may interfere with proper grasping of the dentate ligament and subsequent incision of the cord. The dural flap is sutured to the surrounding muscles. The subarachnoid space is drained relatively dry of cerebrospinal fluid. The dentate ligament is then grasped with a long mosquito hemostat and a single dentation is cut. By passing a septal elevator or blunt nerve hook between the cord and the dentate ligament, one can identify the insertion of the dentate ligament, which is usually marked by a fine, tortuous blood vessel running longitudinally. This is the only point during the operation when the slightest degree of rotation of the cord is made for identification of the insertion of the dentate ligament. The blade is then passed a predetermined depth of $6\frac{1}{4}$ mm. into the cord exactly at the insertion of the dentate ligament. The hemostat attached to the ligament serves thereafter only as counterforce to the forward pull of the blade. Although this maneuver may at times require slight angular placement of the blade because of the confined space, the final position is such that the blade lies at a right angle to the cord. If removal of the bone is carried sufficiently laterally, the blade can be placed at right angles without difficulty. At this point, one has a clear view along the shaft of the knife. The toggle is then drawn toward the operator. When the toggle stops, the blade has passed through a complete arc of 90° and is then drawn laterally (as one would do in drawing a pencil line on paper), care being taken not to withdraw the instrument until it is clear of the cord. It is important that the blade be extremely sharp since increased resistance is encountered in going through the pial envelope. With the blade then at the 180° angle, an additional incision is made 1 to 2 mm. above the dentate insertion to a depth of 1 to 2 mm. continuous with the previous incision to insure section of sacral fibres which may lie above the plane of the dentate ligament. Bleeding from the incision of the cord is controlled by temporary application of Gelfoam or cottonoid pledgets. The dura mater is then approximated with a continuous locked stitch or individual sutures of cotton, the line of incision is overlain with Gelfoam, and the wound is closed in layers.

SUMMARY

Factors accounting for the results of cordotomy are discussed. A technique for cervical cordotomy employing a mechanical knife is described.

We have found that the advantages of this technique are: (1) the ability to produce a more uniformly precise section of a quadrant, (2) the operating time is short-

ened, (3) the postoperative morbidity is reduced, and (4) adequate sensory loss can be obtained.

I am grateful to Mr. John Hastings of Bass River, Massachusetts for his aid in developing the instrument.

ADDENDUM

At present a sharper blade is being developed by the Gillette Razor Blade Company. The instrument is being modified so that this blade can be replaced easily by the individual operator to insure an optimal cutting edge.

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Obituary

WILLIAM JASON MIXTER
1880–1958

Jason Mixter or Dr. Jason, as he was affectionately known by so many of his colleagues, was born of old New England stock in 1880. Like many of the earlier Bostonian physicians, he came from a prominent medical family. His father, Dr. Samuel Jason Mixter, a distinguished surgeon, was a charming, cultured gentleman of the old school with widespread interests which ranged from a deep appreciation of music to breeding of fine dairy cattle, fishing, and hunting. Many of these passed from father to son.

After growing up in Boston and on the farm in Hardwick, he decided to enter his father's *alma mater*, the Massachusetts Institute of Technology, with his brother Charles, rather than Harvard College with the greater proportion of his schoolboy friends. On obtaining an S.B. degree in biology, he entered Harvard Medical School in 1902 and later became a "House Pupil" at the Massachusetts General Hospital. Following the single year then required for intern training he started in private practice with his father and brother. At first both brothers assisted their father and then shared an office for many years. In addition to a busy practice, they often returned to the old family farm in Hardwick, and hunted and fished together. On their early trips to Maine and Alaska they always took their surgical instruments with them and are reputed to have performed a fabulous amount of surgery in the backwoods.

While Jason Mixter's practice of general surgery continued until he was forty, his interest in surgery of the nervous system dates back to 1911. Previously operations on tumours of the brain at the Massachusetts General Hospital had been followed by such a disastrous mortality that Dr. Codman, in his review of end results prior to 1905, concluded that nothing more than a cranial decompression was justified. In 1911 father and son were assigned two hospital beds to try out the new methods being developed by Horsley and Cushing. The newly established assignment prospered and expanded.

With recognition of his ability in this new field, Dr. Mixter continued to serve as visiting surgeon in charge of neurosurgical cases until a special service with him as chief was ultimately established in 1939. In 1926 he and Dr. James B. Ayer, in charge of the neurological patients, were given a combined ward on the ground floor of the old Bulfinch Building. This was shifted to the present neurological-surgical floor when the new surgical building was completed in 1939. Close collaboration with the neurologists, and with the ophthalmologists and orthopaedists as well, proved to be a most fruitful policy. Soon after the opening of the ward in the Bulfinch Building Dr. Mixter was able to convince the hospital trustees of the need for added beds and also to obtain better operating-room facilities, as well as a neurosurgical resident. During the ensuing twenty years 28 young men have had the privilege of training under him. Of these 6 are now full professors and 3 others associate or assistant professors at various university teaching hospitals.

During World War I, two years before the United States entered the conflict, Dr. Mixter went to France as a surgeon attached to the American Ambulance Hospital at Juilly, thirty miles east of Paris, and then nearer the front to the British Red Cross Hospital at Château Annel. After a brief return to the United States he went back again in 1917, this time in uniform with the Massachusetts General Hospital Unit, Base Hospital No. 6, at Talence near Bordeau. A year later he was transferred to England, where he served as Commander of Camp Hospital 35, District Surgeon of the Winchester district, and finally as Commanding Officer of Base Hospital 204 at Hursley Park. This was at the time of the great epidemic of influenza, in which he demonstrated his competence in the field of difficult administrative problems. In World War II, when he was 61, he became Senior Consultant in Neurosurgery to the Surgeon General of the Army from 1941 to 1946.

Dr. Mixter's work as a neurosurgeon was characterized by his skill as an operator in coping with problems, no matter how difficult, in an unruffled and remarkably adaptable fashion (what the French would call "débrouillard"). In addition he had an unusually sympathetic understanding of his patients and personal interest in his house staff. In contrast to the temperamental, difficult personalities of the majority

of neurosurgical pioneers in this country, which often led to frustrating experiences for their medical associates and nurses alike, Dr. Mixter stood out as a singularly lovable human being. With the prominence of Dr. Harvey Cushing at the Peter Bent Brigham Hospital during his earlier years, it was not an easy task to create a second great neurosurgical service in a city as small as Boston. Yet, while Dr. Cushing's contributions to neurosurgery were primarily confined to cerebral tumours, Dr. Mixter's interest spread to the larger fields of treatment of pain, the sympathetic nervous system, and the spinal cord. In association with Dr. Joseph Barr of the Orthopaedic Service, he started his most important work on the problem of low backache with sciatic radiation. They first clarified the syndrome of intervertebral disc protrusion in a paper in 1934 and further described it in a series of classic papers. His bibliography comprises a total of over 60 articles which cover a wide range of general surgical and neurological topics. Together with Walter Dandy and Max Peet, he wrote the sections on neurosurgery for Dean Lewis's *Practice of Surgery*, which appeared in 1932. In addition, with Dr. George Cheever Shattuck, then Professor of Tropical Medicine at Harvard, he wrote a *Handbook of Health for Overseas Service*, published by the Harvard University Press in 1943.

He was elected a member of the American Surgical Association in 1920 and was one of the original members of the Society of Neurological Surgeons. Other medical societies included the American Medical Association, the American College of Surgeons, the American Neurological Association, the Boston Surgical, Harvey Cushing, and New England Neurosurgical Societies. He was one of the five honorary members of the American Academy of Neurosurgery and a past president of the New England Surgical Society. He was also a member of the Corporation of the Massachusetts Institute of Technology from 1944 to 1949 and served as a trustee of the Massachusetts General Hospital from 1946 to 1954.

At the age of 60 in 1940 he had to retire as Chief of the Neurosurgical Service at the Massachusetts General Hospital, but again resumed this post during the war years and continued operating on the private wards until 1953. His interest in the hospital and the neurosurgical service continued undiminished until his final illness. Three years ago his help in raising funds for the research laboratories was the deciding factor in persuading the hospital trustees to build an additional floor to the new pathology building. These laboratories are now named in his honour and he was happily in good health and able to attend the dedication ceremonies when they were opened on October 16th last year. At this time the Rev. Theodore P. Ferris, rector of Trinity Church, summarized Dr. Mixter's unusual personality in this way: "The thing about him that always impressed me most was his kindness. In a polite society you more or less take it for granted that people are kind, especially doctors, but the kindness that I'm talking about is something that you can never take for granted. It is a divine mixture of imaginative awareness and deep concern, a capacity to feel what another person feels, and to care how he feels, what he feels, and that he feels at all." Again, in mentioning his contributions over a period of thirty-nine years as vestryman and senior warden of Trinity Church, Ferris's words are well worth repeating: "We think the young are the ones who are always ready to go out on a limb for a big idea. Dr. Mixter is not young. We think the plain people coming up from the bottom dream the dreams and lead the way. Dr. Mixter is an aristocrat. We think the radicals are the ones who make the improvements in the world. Dr. Mixter is a conservative."

As Dr. Ferris was impressed, all of us who were privileged to work with him soon

came to appreciate that our chief's outstanding quality was a deep, abiding interest in people. This resulted in a host of friends, medical and non-medical as well. The latter included all walks of life from hunters and fishermen to men of affairs and the church.

In 1911 he married Miss Dorothy Fay of Boston. The Mixters were a devoted couple with an unusual number of common interests. Their three sons, a daughter, and numerous nephews and nieces made the family life at the farm in Hardwick and on Cape Cod a singularly pleasant one. His associates at the M.G.H. and medical friends throughout the country, together with a host of former patients, share the loss of a great surgeon, who in addition was a wise counselor and an unusually attractive human being.

JAMES C. WHITE, M.D.

NOTICES

AMERICAN BOARD OF NEUROLOGICAL SURGERY

Examinations were given by the American Board of Neurological Surgery in St. Louis, Missouri, in May 1958, and the following were certified:

ABLIN, GEORGE 2741 "H" St., Bakersfield, Calif.
ADAMETZ, JOHN H. 1014 Donaghey Bldg., Little Rock, Ark.
AMYES, EDWIN W. 3590 Imperial Highway, Lynwood, Calif.
BAKER, ROBERT L. 4035 Jenkins Arcade, Pittsburgh, Pa.
BATTISTA, ARTHUR F. 550 First Ave., New York 16, N. Y.
CHOU, SHELLEY N. 975 E. 1st South St., Salt Lake City 2, Utah
CLARK, ROBERT A. 750 Hemlock St., Macon, Ga.
GLASS, BERNARD 814 National Bank Bldg., Lima, Ohio
HUANG, SHI HUI (Foreign) Dept. of Surgery, School of Medicine, National Taiwan University, Taipei, Formosa
HUSTON, WILLIAM W. 10628 Riverside Dr., North Hollywood, Calif.
IWATA, KINJIRO (Foreign) Nagoya University School of Medicine, Nagoya, Japan
LATIMER, FREDERICK R. 1010 Mutual Bldg., Detroit 26, Mich.
LEE, HUN JAE (Foreign) Youn Sei University Medical College, Seoul, Korea
MCGUIRE, THOMAS H. 720 Medical Arts Bldg., Houston, Texas
MARK, VERNON H. Massachusetts General Hospital, Boston, Mass.
MEAD, PERRY A. Anchorage, Alaska
MORA, FEDERICO (Foreign) 17 Ave. 18-66, Zona 10, Guatemala City, Guatemala
OLIVE, J. IGNACIO (Foreign) Niza 46, Mexico 6, D. F.
PENKA, ERNEST J. c/o Bureau of Medicine & Surgery, U. S. Navy, Washington 25, D. C.
PITTMAN, HAL W. 550 W. Thomas Road, Phoenix, Ariz.
PORTER, ROBERT W. 5901 E. 7th St., Long Beach, Calif.
TYTUS, JOHN S. Mason Clinic, 118 9th Ave., Seattle 1, Wash.

AMERICAN NEUROLOGICAL ASSOCIATION

At the 83rd annual meeting of the American Neurological Association held in Atlantic City, New Jersey on June 16–18, 1958, the following officers were elected for the coming year: President, Bernard J. Alpers, Philadelphia, Pa.; President-Elect, Derek Denny-Brown, Boston, Mass.; 1st Vice-President, Paul I. Yakovlev, Boston, Mass.; 2nd Vice-President, Margaret A. Kennard, Ft. Steilacoom, Wash.; Secretary-Treasurer, Charles Rupp, Philadelphia, Pa.; Assistant Secretary, William F. Caveness, New York, N. Y., and Editor of Transactions, Charles Rupp.

The 84th annual meeting of the Association will be held at the Claridge Hotel, Atlantic City, New Jersey, June 15–17, 1959.

INTERNATIONAL CONGRESS OF NEUROLOGICAL SURGERY

The Second International Congress of Neurological Surgery will be held in Washington, D. C. from October 14 to 20, 1961. The Statler Hotel will be the headquarters for the Congress and all scientific meetings will be held there. The business meeting of the Executive Committee, which is composed of two delegates from each of the member-societies, will be held on Saturday, October 14, 1961. The registration and reception will be held on Sunday, October 15, 1961, and the scientific sessions will be held from Monday, October 16, to Friday, October 20.

The American Express Company has been selected as the official travel agents for the Congress. They have agreed to accept local currencies in payment for

transportation to and from the Congress and within the United States and for hotel accommodations, rooms, meals, etc., reserved prior to departure for the Congress. These arrangements will be available at the offices and agencies of the American Express Company throughout the world.

Further details regarding the Second International Congress of Neurological Surgery will be published from time to time.

MEETINGS

American Academy of Neurological Surgery, Royal York Hotel, Toronto, Canada, Nov. 6–8, 1958. Dr. Robert McLaurin, Cincinnati General Hospital, Cincinnati 29, Ohio, Secretary.

American Neurological Association, Claridge Hotel, Atlantic City, N. J., June 15–17, 1959. Dr. Charles Rupp, 133 South 36th St., Philadelphia, Pa., Secretary.

Association for Research in Nervous and Mental Disease, Hotel Roosevelt, New York City, Dec. 12–13, 1958. Dr. Rollo J. Masselink, 700 West 168th St., New York 32, N. Y., Secretary. (Subject: Neuromuscular disorders.)

Chilean Society of Neurosurgery, Santiago, Chile, Sept. 12–13, 1958. Dr. Juan Fierro M., Secretary-General.

Congress of Neurological Surgeons, St. Francis Hotel, San Francisco, Calif., Oct. 30–Nov. 1, 1958. Dr. Richard DeSaussure, Jr., 525 Physicians & Surgeons Bldg., Memphis 3, Tenn., Secretary.

Harvey Cushing Society, Roosevelt Hotel, New Orleans, La., April 30–May 2, 1959. Dr. David L. Reeves, 316 West Junipero St., Santa Barbara, Calif., Secretary.

International Congress of Neurological Surgery (II), Statler Hotel, Washington, D. C., Oct. 14–20, 1961. Dr. Bronson S. Ray, 525 East 68th St., New York 21, N. Y., Secretary-General.

Latin American Congress of Neurosurgery, Santiago, Chile, April 12–15, 1959. Dr. Alfonso Asenjo, Casilla 70 D, Santiago, Chile, Secretary-General.

Neurosurgical Society of America, The Homestead, Hot Springs, Va., March 4–7, 1959. Dr. Frank P. Smith, 260 Crittenden Blvd., Rochester 20, N. Y., Secretary.

Southern Neurosurgical Society, Americana, Bal Harbor, Miami Beach, Fla., Jan. 23–24, 1959. Dr. C. D. Hawkes, 22 N. Manassas St., Memphis 5, Tenn., Secretary.

Western Neurosurgical Society, Del Monte Lodge, Pebble Beach, Calif., Oct. 20–22, 1958. Dr. Ernest W. Mack, 505 S. Arlington Ave., Reno, Nev., Secretary.

JOURNAL OF NEUROSURGERY

The *Journal of Neurosurgery* is devoted to the publication of work relating primarily to neurosurgery, including studies in clinical neurophysiology, organic neurology, ophthalmology, radiology and pathology. Short articles on unusual cases and on technique, special instruments or equipment that might be useful to others in the field are also acceptable.

MANUSCRIPTS are accepted with the understanding that they are contributed solely for publication in this *Journal.* They should be addressed to Dr. Louise Eisenhardt, 333 Cedar Street, New Haven 11, Connecticut, U.S.A. They should be typewritten in double space, with tabular matter and passages for small print on separate sheets. All materials should be mailed flat.

REFERENCES should be arranged alphabetically and cited by superior numerals in the text. The following order should be used:

Articles: Name of author, full title of article, name of periodical, year, volume, first and last page of article. Abbreviations of names of periodicals should conform to the style used in *World list of scientific periodicals published in the years 1900–1950* (London: Butterworths Scientific Publications, 1952).

Books: Name of author, full title of book, city, publisher, year, edition, full pagination (if book is in more than one volume, give the number of volumes).

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